

## Novel Hyaluronan-Binding Proteins and Encoding Genes

### *Field of the Invention*

5 This application claims benefit under 35 U.S.C. § 119(e) of the filing date of copending U.S. Provisional Application Serial No. 60/113,871 filed on December 23, 1998, which is hereby incorporated by reference in its entirety.

10 The present invention relates to a novel member of the Hyaluronan-binding protein family, the full-length WF-HABP protein. More specifically, the present invention relates to the discovery, identification and characterization of nucleotides that encode full-length WF-HABP. The invention encompasses full-length WF-HABP polynucleotides; host cell expression systems; encompasses full-length WF-HABP polypeptides (including fragments, variants, derivatives and analogs thereof); encompasses full-length WF-HABP fusion proteins; antibodies encompasses full-length WF-HABP; agonists and antagonists encompasses full-length WF-HABP; and  
15 other compounds that modulate encompasses full-length WF-HABP gene expression or encompasses full-length WF-HABP activity; that can be used for diagnosis, drug screening, and treatment or prevention of disorders which include, but are not limited to, vascular disorders and conditions, congenital pain insensitivity, inflammation, ischemia, host defense dysfunction, immune surveillance dysfunction, neural disorders, arthritis, edema, multiple sclerosis, autoimmunity, immune dysfunction,  
20 cancers, metastasis, integumentary disorders, and allergy.

The present invention relates to a novel member of the Hyaluronan-binding protein family, the WF-HABP protein. More specifically, the present invention relates to the discovery, identification and characterization of nucleotides that encode WF-HABP.  
25 HABP. The invention encompasses WF-HABP polynucleotides; host cell expression systems; WF-HABP polypeptides (including fragments, variants, derivatives and analogs thereof); WF-HABP fusion proteins; antibodies to WF-HABP; agonists and antagonists of WF-HABP; and other compounds that modulate WF-HABP gene expression or WF-HABP activity; that can be used for diagnosis, drug screening, and  
30 treatment or prevention of disorders which include, but are not limited to, vascular disorders and conditions, congenital pain insensitivity, inflammation, ischemia, host defense dysfunction, immune surveillance dysfunction, neural disorders, arthritis, edema, multiple sclerosis, autoimmunity, immune dysfunction, cancers, metastasis, integumentary disorders, and allergy.

35 The present invention relates to a novel member of the Hyaluronan-binding protein family, the OE-HABP protein. More specifically, the present invention relates

to the discovery, identification and characterization of nucleotides that encode OE-HABP. The invention encompasses OE-HABP polynucleotides; host cell expression systems; OE-HABP polypeptides (including fragments, variants, derivatives and analogs thereof); OE-HABP fusion proteins; antibodies OE-HABP; agonists and antagonists of OE-HABP; and other compounds that OE-HABP gene expression or OE-HABP activity; that can be used for diagnosis, drug screening, and treatment or prevention of disorders which include, but are not limited to, vascular disorders and conditions, congenital pain insensitivity, inflammation, ischemia, host defense dysfunction, immune surveillance dysfunction, neural disorders, arthritis, edema, multiple sclerosis, autoimmunity, immune dysfunction, cancers, metastasis, integumentary disorders, and allergy.

The present invention relates to a novel member of the Hyaluronan-binding protein family, the BM-HABP protein. More specifically, the present invention relates to the discovery, identification and characterization of nucleotides that encode BM-HABP. The invention encompasses BM-HABP polynucleotides; host cell expression systems; BM-HABP polypeptides (including fragments, variants, derivatives and analogs thereof); BM-HABP fusion proteins; antibodies BM-HABP; agonists and antagonists of BM-HABP; and other compounds that BM-HABP gene expression or BM-HABP activity; that can be used for diagnosis, drug screening, and treatment or prevention of disorders which include, but are not limited to, vascular disorders and conditions, congenital pain insensitivity, inflammation, ischemia, host defense dysfunction, immune surveillance dysfunction, neural disorders, arthritis, edema, multiple sclerosis, autoimmunity, immune dysfunction, cancers, metastasis, integumentary disorders, and allergy.

### ***Background of the Invention***

Hyaluronan (HA, hyaluronate, hyaluronan, hyaluronic acid) is a negatively charged, high molecular weight, connective tissue polysaccharide found in the extracellular matrix of most animal tissues. HA consists of alternating N-acetyl-D-glucosamine and D-glucuronic acid residues linked by B(1-4) and B (1-3) bonds which has a molecular weight ranging from 1 and  $50 \times 10^6$  Da (Brimacombe, JS., et al., in Mucopolysaccharides. (Elsevier, Amsterdam, 1964)) depending upon its source. For example, its has been determined that HA averages between  $3-5 \times 10^6$  Da, or  $6-7 \times 10^6$  Da, when isolated from rheumatoid fluid, or normal synovial fluid, respectively (Laurent, TC, et al., Immunol Cell Biol., 74:1-7, (1996)). In addition, dilute solutions of HA ( $< 1 \text{ mg/mL}$ ) are known to result in highly entangled networks which instill unique rheological characteristics to the solution in hand (Laurent, TC., Immuno Cell

Biol., 74:1-7, (1996)). For example, solutions of hyaluronan are viscoelastic with the viscosity maintaining a pronounced dependency on shear forces (Ogston, AG., et al., J. Physiol., 199:244-52, (1953)). Therefore, considering the increased localization of HA in the body between surfaces that move against each other, combined with the mechanical/physical characteristics ascribed above, HA has been attributed the primary role of lubrication and protection of joints and tissues, cartilage surfaces and muscle bundles. Further, HA has also been associated with the scavenging of free radicals and debris (Myint, P., et al., Biochim. Biophys. Acta, 925:194-202, (1987), and Laurent, TC, Ann. Rheum. Dis., 54:429-32, (1995), respectively), keeping the joint cavities open (Edwards, JCW., et al., J. Anat., 185:355-67, 1994), forming flow barriers in the synovium (McDonald, JN., et al., J. Physiol., 485.1:179-93, (1995)), and the prevention of capillary growth (Sattar, A., Semin. Arthritis Rheum., 22:37-43, (1992)).

HA is synthesized ubiquitously in the plasma membrane of all vertebrate tissues and in some bacteria (Fraser, JRE, J. Intern Med., 242:27-33, (1997)). It is catabolized locally through receptor-mediated endocytosis and lysosomal degradation, in addition to, the lymph nodes and endothelial cells of the liver sinusoids. HA is commonly isolated from the vitreous body of the eye, synovial fluid, rheumatoid fluid, umbilical cord, and skin. Several physiological functions have been associated with HA, in particular water homeostasis; mitosis, cell migration, differentiation, angiogenesis (Rooney P and Kumar S (1994) EXS (Switzerland) 70:179-90); and tissue remodeling, both in normal or tumor-associated events. Its role in water homeostasis (resistance to bulk flow of solvent) is particularly important as it has been shown to prevent excessive fluid exchange between tissue compartments, during both normal conditions and injury (Day, TD., Nature, 166:785-6., (1950)). In addition, HA is thought to play an important role in the promotion of cell proliferation and migration during tissue development and regeneration (Toole, BP., in Cell Biology of Extracellular Matrix (Hay ED, ed), pp.305-339 (Plenum Press, New York, (1991)).

The matrix-induced effects on cells are directed by a wide variety of HA-binding proteins which are classified into two groups: structural (matrix) and cell-surface-associated (HA-receptors) (Tool, BP., Curr Opin Cell Biol 2:839-844 (1990)). The widespread occurrence of HRs indicate their importance in tissue organization and control of cellular behavior. The family is known as the hyaladherins and includes those RA-binding proteins which act as part of the structural matrix and those which interact with HA at the plasma membrane as cell-surface matrix receptors. Although not comprehensive, some of the identified members of the hyaladherin family include aggrecan, link protein (Manuskiatti, W., Int J Dermatology, 35(8):539-533, (1996)),

versican, hyaluronectin, neurocan (Knudson, CB et al., FASEB J, 7:1233-1241, (1993)), CD44 family of receptors (Underhill, CB., J Cell Sci.), RHAMM (Receptor for Hyaluronan-Mediated Motility), and TSG-6 (Tumor Necrosis Factor-Stimulated Gene 6). With the recognition of the Hyaluronan cell-surface receptor (HR), cell biologists, pathologists, and immunologists have begun to investigate the importance of the HA and HR for their potential diagnostic and therapeutic value.

HRs found within the cartilage matrix have been well characterized. Aggrecan is the large aggregating chondroitin sulfate proteoglycan of cartilage which has a high affinity for HA (Hardingham et al, Biochim Biophys. Acta., 279:401-405, (1972)). Link protein is a 45-48 kDa glycoprotein which also demonstrates strong specific binding affinity. HA may bind more than 100 aggrecan and link protein molecules in a supramolecular complex which confers the viscoelastic properties of cartilage. Other matrix proteins such as PG-M and type VI collagen which participate in assembly and integrity may also be involved.

HA-binding proteins are also found in noncartilaginous tissues. Versican of fibroblasts, hyaluronectin of nervous and soft connective tissues, glial hyaluronan binding protein in the central nervous system, and neurocan, a chondroitin sulfate proteoglycan of brain, also form strong structural complexes with HA. All matrix hyaloadherins contain tandem repeated B loops, a structural motif believed to contain the HA-binding domain.

HR hyaloadherins have been detected on several cell types from a wide variety of tissues based upon hyaluronans ability to aggregate such cells (Pessac, B., et al., Science, 175:898-900, (1972)). Some reports suggest that HRs are related to the CD44 family of lymphocyte homing receptors which include the isoforms, Pgp-1, Hermes antigen, H-CAM and ECMRIII. The distal extracellular domain of CD44 has sequence homology to one of the B loop motifs of link protein. The numerous isoforms suggest different cellular functions and demonstrate binding to other ligands such as collagens I and IV and mucosal vascular addressing. Further, although many roles have been attributed to the CD44-hyaluronan interaction, its roles in development, tumour progression, and in the immune response appear to be the most prevalent (Sherman, L., Curr. Opinion Cell Biol., 6:726-33, (1994).

Other non-CD44 HRs include cell-surface antigens termed IVd4 which block binding of HA, liver endothelial cell receptors (LEC) which are involved in the clearance of HA from the circulation, and fibroblast-produced HR which may be located on the cell surface where it mediates HA-induced cell locomotion. Its 58 kDa soluble form contains an HA-binding component unrelated to the B loop motif and is known as a receptor for HA mediated motility (RHAMM). The important distinctions



between cell-surface and matrix hyaloadherins are 1) HA hexasaccharides represent the minimum size molecule that interacts with these cell-surface receptors, 2) binding affinity increases with increasing polymer length, and 3) binding increases with increasing buffer ionic strength.

5 Increased matrix presence of HA has been correlated with cell migration in embryogenesis, limb regeneration, wound healing and tumor invasion. Since the CD44 HR have been shown to associate with cytoskeletal ankyrin, proteins of the HR complex may affect re-organization of the actin cytoskeleton and other activities such as cell ruffling, detachment from the substratum, and locomotion necessary for cell  
10 migration. RHAMM, as one of the HR complex proteins, binds to HA with high affinity and is expressed only in the leading lamellae and perinuclear regions of migrating fibroblasts.

Since RHAMM does not include a transmembrane hydrophobic region, it is assumed to be a peripheral protein associated with intracellular, membrane bound  
15 tyrosine kinase. In studies of timed administration of HA and an inhibitor of tyrosine kinase, HA stimulated locomotion via a rapid tyrosine kinase signal transduction pathway.

Invasive or metastatic cancer cells have the capacity to exit from the vascular system by use of sets of molecules, at least one of which always has a receptor  
20 function. One series of such sets might include successive interactions among endothelial VLA-4 integrin and E-selectin, subendothelial collagen IV and B-4 integrin, and soft connective tissue HA and CD44 or HR interactions (Zetter BR (1993) Semin Cancer Biol 4:215-218).

Some tumor cells also have the capacity to assemble HA-enriched pericellular  
25 matrices which reduce cell adhesion to the outside of the growing tumor and protect the tumor from immune surveillance. In addition, the presence of high HA attracts endothelial cells which are active in angiogenesis. The combination of these HA functions allows the rapid establishment and growth of invasive tumor cells.

The transforming oncogene H-ras may promote cell locomotion. Hardwick et al  
30 (1992 J Cell Biol 117:1343-1350) reported that H-ras actually regulates expression of RHAMM, showed binding between HA and RHAMM, and produced an antibody to the protein which is capable of inhibiting HA/HR locomotion.

The fact that WF-HABP, OE-HABP, and BM-HABP polynucleotides and polypeptides are members of the hyaluronan receptor family suggests that: invention  
35 would play an important role in diverse human disease states ranging from inflammatory conditions to, cancer metastasis, and more generally that members of this family mediate cellular responses such as activation, survival, proliferation, migration,

signalling, and differentiation; that hyaluronan receptor family members provide an important model system for the *in vitro* study of arthritis, angiogenesis, and hematopoietic or immune disorders; and that hyaluronan receptors would provide defined targets for the development of new anti-cancer, arthritis, and healing wound tissue agents.

### Summary of the Invention

The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding the full-length WF-HABP having the amino acid sequence shown in Figures 1A-H (SEQ ID NO:2) or the amino acid sequence encoded by the cDNA clone encoding full-length WF-HABP. The present invention also relates to recombinant vectors, which include the isolated nucleic acid molecules of the present invention, and to host cells containing the recombinant vectors, as well as to methods of making such vectors and host cells and for using them or other genetically modified host cells to produce full-length WF-HABP polypeptides (including fragments, variants, derivatives, and analogs thereof) by recombinant techniques.

The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding the WF-HABP having the amino acid sequence shown in Figures 2A-B (SEQ ID NO:5) or the amino acid sequence encoded by the cDNA clone encoding WF-HABP deposited in a vector as ATCC Deposit Number 203503 December 1, 1998. The present invention also relates to recombinant vectors, which include the isolated nucleic acid molecules of the present invention, and to host cells containing the recombinant vectors, as well as to methods of making such vectors and host cells and for using them or other genetically modified host cells to WF-HABP polypeptides (including fragments, variants, derivatives, and analogs thereof) by recombinant techniques.

The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding OE-HABP having the amino acid sequence shown in Figures 3A-B (SEQ ID NO:8) or the amino acid sequence encoded by the cDNA clone encoding OE-HABP deposited in a vector as ATCC Deposit Number 203501 on December 1, 1998. The present invention also relates to recombinant vectors, which include the isolated nucleic acid molecules of the present invention, and to host cells containing the recombinant vectors, as well as to methods of making such vectors and host cells and for using them or other genetically modified host cells to produce OE-HABP polypeptides (including fragments, variants, derivatives, and analogs thereof) by recombinant techniques.

The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding BM-HABP having the amino acid sequence shown in Figures 4A-B (SEQ ID NO:11) or the amino acid sequence encoded by the cDNA clone encoding BM-HABP deposited in a vector as ATCC Deposit Number 203502 on December 1, 1998. The present invention also relates to recombinant vectors, which include the isolated nucleic acid molecules of the present invention, and to host cells containing the recombinant vectors, as well as to methods of making such vectors and host cells and for using them or other genetically modified host cells to produce BM-HABP polypeptides (including fragments, variants, derivatives, and analogs thereof) by recombinant techniques.

The invention further provides isolated full-length WF-HABP polypeptides having amino acid sequences encoded by the polynucleotides described herein.

The invention further provides isolated WF-HABP polypeptides having amino acid sequences encoded by the polynucleotides described herein.

The invention further provides isolated OE-HABP polypeptides having amino acid sequences encoded by the polynucleotides described herein.

The invention further provides isolated BM-HABP polypeptides having amino acid sequences encoded by the polynucleotides described herein.

The present invention also provides a screening method for identifying compounds capable of eliciting a cellular response induced by the full-length WF-HABP, which involves contacting cells which express WF-HABP with the candidate compound, assaying a cellular response (e.g., ion flux, , cellular proliferation, cellular migration, cell adhesion, etc.), and comparing the cellular response to a standard cellular response, the standard being assayed in absence of the candidate compound; whereby, an increased cellular response over the standard indicates that the compound is an agonist.

The present invention also provides a screening method for identifying compounds capable of eliciting a cellular response induced by WF-HABP, which involves contacting cells which express WF-HABP with the candidate compound, assaying a cellular response (e.g., ion flux, , cellular proliferation, cellular migration, cell adhesion, etc.), and comparing the cellular response to a standard cellular response, the standard being assayed in absence of the candidate compound; whereby, an increased cellular response over the standard indicates that the compound is an agonist.

The present invention also provides a screening method for identifying compounds capable of eliciting a cellular response induced by OE-HABP, which involves contacting cells which express OE-HABP with the candidate compound, assaying a cellular response (e.g., ion flux, , cellular proliferation, cellular migration,

cell adhesion, etc.), and comparing the cellular response to a standard cellular response, the standard being assayed in absence of the candidate compound; whereby, an increased cellular response over the standard indicates that the compound is an agonist.

5 The present invention also provides a screening method for identifying compounds capable of eliciting a cellular response induced by BM-HABP, which involves contacting cells which express BM-HABP with the candidate compound, assaying a cellular response (e.g., ion flux, , cellular proliferation, cellular migration, cell adhesion, etc.), and comparing the cellular response to a standard cellular response, the standard being assayed in absence of the candidate compound; whereby, an  
10 increased cellular response over the standard indicates that the compound is an agonist.

The present invention also provides a screening method for identifying compounds capable of enhancing or inhibiting a cellular response induced by the full-length WF-HABP receptors, which involves contacting cells which express full-length WF-HABP receptors with the candidate compound in the presence of a full-length WF-  
15 HABP agonist (e.g., hyaluronan) or other stimulus (e.g., injury, or IL-1b or TNF-a induction), assaying a cellular response (e.g., ion flux, , cellular proliferation, cellular migration, cell adhesion, etc. ), and comparing the cellular response to a standard cellular response, the standard being assayed when contact is made between the agonist and full-length WF-HABP or when full-length WF-HABP is exposed to the stimulus,  
20 in absence of the candidate compound; whereby, an increased cellular response over the standard indicates that the compound is an agonist and a decreased cellular response over the standard indicates that the compound is an antagonist.

The present invention also provides a screening method for identifying compounds capable of enhancing or inhibiting a cellular response induced by WF-  
25 HABP receptors, which involves contacting cells which express WF-HABP receptors with the candidate compound in the presence of a WF-HABP agonist (e.g., hyaluronan) or other stimulus (e.g., injury, or IL-1b or TNF-a induction), assaying a cellular response (e.g., ion flux, , cellular proliferation, cellular migration, cell adhesion, etc. ), and comparing the cellular response to a standard cellular response, the  
30 standard being assayed when contact is made between the agonist and WF-HABP or when WF-HABP is exposed to the stimulus, in absence of the candidate compound; whereby, an increased cellular response over the standard indicates that the compound is an agonist and a decreased cellular response over the standard indicates that the compound is an antagonist.

35 The present invention also provides a screening method for identifying compounds capable of enhancing or inhibiting a cellular response induced by OE-HABP receptors, which involves contacting cells which express OE-HABP receptors

with the candidate compound in the presence of a OE-HABP agonist (e.g., hyaluronan) or other stimulus (e.g., injury, or IL-1b or TNF-a induction), assaying a cellular response (e.g., ion flux, such as, cellular proliferation, cellular migration, cell adhesion, etc.), and comparing the cellular response to a standard cellular response, the standard being assayed when contact is made between the agonist and OE-HABP or when OE-HABP is exposed to the stimulus, in absence of the candidate compound; whereby, an increased cellular response over the standard indicates that the compound is an agonist and a decreased cellular response over the standard indicates that the compound is an antagonist.

The present invention also provides a screening method for identifying compounds capable of enhancing or inhibiting a cellular response induced by BM-HABP receptors, which involves contacting cells which express BM-HABP receptors with the candidate compound in the presence of a BM-HABP agonist (e.g., hyaluronan) or other stimulus (e.g., injury, or IL-1b or TNF-a induction), assaying a cellular response (e.g., ion flux, cellular proliferation, cellular migration, cell adhesion, etc.), and comparing the cellular response to a standard cellular response, the standard being assayed when contact is made between the agonist and BM-HABP or when BM-HABP is exposed to the stimulus, in absence of the candidate compound; whereby, an increased cellular response over the standard indicates that the compound is an agonist and a decreased cellular response over the standard indicates that the compound is an antagonist.

In another embodiment, a screening assay for agonists and antagonists is provided which involves determining the effect a candidate compound has on the binding of cellular ligands (e.g., hyaluronan, chondroitin-sulfate proteoglycans, etc.) to full-length WF-HABP. In particular, the method involves contacting full-length WF-HABP with a ligand or other stimulus (e.g., injury, or IL-1b or TNF-a induction) and a candidate compound and determining whether ligand binding to full-length WF-HABPs is increased or decreased due to the presence of the candidate compound.

In another embodiment, a screening assay for agonists and antagonists is provided which involves determining the effect a candidate compound has on the binding of cellular ligands (e.g., hyaluronan, chondroitin-sulfate proteoglycans, etc.) to WF-HABP. In particular, the method involves contacting WF-HABP with a ligand or other stimulus (e.g., injury, or IL-1b or TNF-a induction) and a candidate compound and determining whether ligand binding to WF-HABPs is increased or decreased due to the presence of the candidate compound.

In another embodiment, a screening assay for agonists and antagonists is provided which involves determining the effect a candidate compound has on the

binding of cellular ligands (e.g., hyaluronan, chondroitin-sulfate proteoglycans, etc.) to OE-HABP. In particular, the method involves contacting OE-HABP with a ligand or other stimulus (e.g., injury, or IL-1b or TNF-a induction) and a candidate compound and determining whether ligand binding to OE-HABPs is increased or decreased due to the presence of the candidate compound.

In another embodiment, a screening assay for agonists and antagonists is provided which involves determining the effect a candidate compound has on the binding of cellular ligands (e.g., hyaluronan, chondroitin-sulfate proteoglycans, etc.) to BM-HABP. In particular, the method involves contacting BM-HABP with a ligand or other stimulus (e.g., injury, or IL-1b or TNF-a induction) and a candidate compound and determining whether ligand binding to BM-HABPs is increased or decreased due to the presence of the candidate compound.

The invention further provides a diagnostic method useful during diagnosis or prognosis of disease states resulting from aberrant cell secretion, activation, survival, migration, differentiation and/or proliferation, due to alterations in full-length WF-HABP coding sequences and/or receptor expression.

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The invention further provides a diagnostic method useful during diagnosis or prognosis of disease states resulting from aberrant cell secretion, activation, survival, migration, differentiation and/or proliferation, due to alterations in OE-HABP coding sequences and/or receptor expression.

The invention further provides a diagnostic method useful during diagnosis or prognosis of disease states resulting from aberrant cell secretion, activation, survival, migration, differentiation and/or proliferation, due to alterations in BM-HABP coding sequences and/or receptor expression.

An additional embodiment of the invention is related to a method for treating an individual in need of an increased level of full-length WF-HABP activity in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of full-length WF-HABP polypeptides or polynucleotides of the invention or a full-length WF-HABP agonist.

An additional embodiment of the invention is related to a method for treating an individual in need of an increased level of WF-HABP activity in the body comprising administering to such an individual a composition comprising a therapeutically effective

amount of WF-HABP polypeptides or polynucleotides of the invention or a WF-HABP agonist.

5 An additional embodiment of the invention is related to a method for treating an individual in need of an increased level of OE-HABP activity in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of OE-HABP polypeptides or polynucleotides of the invention or a OE-HABP agonist.

10 An additional embodiment of the invention is related to a method for treating an individual in need of an increased level of BM-HABP activity in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of BM-HABP polypeptides or polynucleotides of the invention or a BM-HABP agonist.

15 A still further embodiment of the invention is related to a method for treating an individual in need of a decreased level of a full-length WF-HABP receptor activity in the body comprising, administering to such an individual a composition comprising a therapeutically effective amount of full-length WF-HABP polypeptides or polynucleotides of the invention a full-length WF-HABP antagonist.

20 A still further embodiment of the invention is related to a method for treating an individual in need of a decreased level of a WF-HABP receptor activity in the body comprising, administering to such an individual a composition comprising a therapeutically effective amount of WF-HABP polypeptides or polynucleotides of the invention a WF-HABP antagonist.

25 A still further embodiment of the invention is related to a method for treating an individual in need of a decreased level of a OE-HABP receptor activity in the body comprising, administering to such an individual a composition comprising a therapeutically effective amount of OE-HABP polypeptides or polynucleotides of the invention a OE-HABP antagonist.

30 A still further embodiment of the invention is related to a method for treating an individual in need of a decreased level of a BM-HABP receptor activity in the body comprising, administering to such an individual a composition comprising a therapeutically effective amount of BM-HABP polypeptides or polynucleotides of the invention a BM-HABP antagonist.

35 The invention additionally provides soluble forms of the polypeptides of the present invention. Soluble peptides are defined by amino acid sequences wherein the sequence comprises the polypeptide sequence lacking a transmembrane domain (e.g., full-length WF-HABP polypeptide fragments corresponding to intracellular and/or

extracellular domains). Such soluble forms of full-length WF-HABP are useful as antagonists of the membrane bound forms of the receptor.

5 The invention additionally provides soluble forms of the polypeptides of the present invention. Soluble peptides are defined by amino acid sequences wherein the sequence comprises the polypeptide sequence lacking a transmembrane domain (e.g., WF-HABP polypeptide fragments corresponding to intracellular and/or extracellular domains). Such soluble forms of WF-HABP are useful as antagonists of the membrane bound forms of the receptor.

10 The invention additionally provides soluble forms of the polypeptides of the present invention. Soluble peptides are defined by amino acid sequences wherein the sequence comprises the polypeptide sequence lacking a transmembrane domain (e.g., OE-HABP polypeptide fragments corresponding to intracellular and/or extracellular domains). Such soluble forms of OE-HABP are useful as antagonists of the membrane bound forms of the receptor.

15 The invention additionally provides soluble forms of the polypeptides of the present invention. Soluble peptides are defined by amino acid sequences wherein the sequence comprises the polypeptide sequence lacking a transmembrane domain (e.g., BM-HABP polypeptide fragments corresponding to intracellular and/or extracellular domains). Such soluble forms of BM-HABP are useful as antagonists of the membrane bound forms of the receptor.

### Brief Description of the Figures

25 Figures 1A-H show the nucleotide sequence (SEQ ID NO:1) and deduced amino acid sequence (SEQ ID NO:2) of the full-length WF-HABP. The deduced complete amino acid sequence includes 2157 amino acid residues and has a deduced molecular weight of about 231657.63 Da. The predicted domains of the WF-HABP polypeptide are: an HA binding motif (amino acid residues E-1791 to C-1894 of SEQ ID NO:2), double underlined; EGF-like Type 1 domains (amino acid residues from C-375 to C-386, amino acid residues from C-943 to C-954, amino acid residues from C-987 to C-998, , amino acid residues from C-1582 to C-1593, and amino acid residues from C-1626 to C-1637 of SEQ ID NO:2), indicated by “~” above the line; EGF-like Type 2 domains (amino acid residues from C-465 to C-478, amino acid residues from C-508 to C-521, amino acid residues from C-551 to C-564, amino acid residues from C-943 to C-957, amino acid residues from C-987 to C-998, amino acid residues from C-1027 to C-1040, amino acid residues from C-1069 to C-1082, amino acid residues from C-1111 to C-1125, amino acid residues from C-1582 to C-1596, amino acid residues from C-1582 to C-1596, amino acid residues from C-1626 to C-1637, amino



acid residues from C-1663 to C-1676, amino acid residues from C-1747 to C-1760, and amino acid residues from C-1894 to C-1908 of SEQ ID NO:2), dashed-underline; laminin-type EGF domain (amino acid residues from C-943 to C-977, and amino acid residues from C-1582 to C-1616 of SEQ ID NO:2), italicized; link protein domain (amino acid residues from C-1817 to C-1862 of SEQ ID NO:2), "\*" above the line; cytochrome P450 cysteine heme-iron ligand binding domains (amino acid residues from F-344 to G-353, and amino acid residues from W-514 to A-523 of SEQ ID NO:2), lower case letters; prokaryotic membrane lipoprotein lipid attachment site domains (amino acid residues from P-1103 to C-1113, and amino acid residues from T-1405 to C-1415 of SEQ ID NO:2), strikethrough letters.

Figures 2A-B show the nucleotide sequence (SEQ ID NO:4) and deduced amino acid sequence (SEQ ID NO:5) of WF-HABP. The deduced complete amino acid sequence includes 457 amino acid residues and has a deduced molecular weight of about 48448.90 Da. The predicted domains of the WF-HABP polypeptide are: an HA binding domain (amino acid residues E-91 to C-194 of SEQ ID NO:5), double underlined; EGF-like Type 2 domain (amino acid residues C-194 to C-208, of SEQ ID NO:5), dashed-underline; and a link domain domain (amino acid residues C-117 to C-162, of SEQ ID NO:5), "\*" above the line.

Figures 3A-B show the nucleotide sequence (SEQ ID NO:7) and deduced amino acid sequence (SEQ ID NO:8) of OE-HABP. The deduced complete amino acid sequence includes 289 amino acid residues and has a deduced molecular weight of about 33174.55 Da. The predicted domains of the OE-HABP polypeptide are: an HA binding motif domain (amino acid residues P-97 to F-168, amino acid residues L-209 to C-286, of SEQ ID NO:8), double underlined; and a link protein domain (amino acid residues C-188 to C-233 of SEQ ID NO:8), "\*" above the line.

*Sub B1* Figures 4A-B show the nucleotide sequence (SEQ ID NO:10) and deduced amino acid sequence (SEQ ID NO:11) of BM-HABP. The deduced complete amino acid sequence includes 353 amino acid residues and has a deduced molecular weight of about 36063.32 Da. The predicted domains of the BM-HABP polypeptide are: an HA binding motif domain (amino acid residues Q-121 to L-215 in (SEQ ID NP:11)), double underlined.

Figures 5A-G shows the regions of identity between the amino acid sequence of the full-length WF-HABP protein (SEQ ID NO:2) and the translation product of the human TSG-6 protein (See Genbank Accession No. gil339994), as determined by Megalign (DNA Star suite of programs) analysis. Identical amino acids between the two polypeptides are shaded, while the non-identical regions remain unshaded. By

examining the regions of amino acids shaded and/or unshaded, the skilled artisan can readily identify conserved domains between the two polypeptides.

Figures 6A-B shows the regions of identity between the amino acid sequence of the WF-HABP protein (SEQ ID NO:5) and the translation product of the human TSG-6 protein (See Genbank Accession No. gil339994), as determined by Megalign (DNA Star suite of programs) analysis. Identical amino acids between the two polypeptides are shaded, while the non-identical regions remain unshaded. By examining the regions of amino acids shaded and/or unshaded, the skilled artisan can readily identify conserved domains between the two polypeptides.

Figures 7 shows the regions of identity between the amino acid sequence of the OE-HABP protein (SEQ ID NO:8) and the translation product of the Cartilage Link Protein from Gallus gallus (See Genbank Accession No. gil212260), as determined by Megalign (DNA Star suite of programs) analysis. Identical amino acids between the two polypeptides are shaded, while the non-identical regions remain unshaded. By examining the regions of amino acids shaded and/or unshaded, the skilled artisan can readily identify conserved domains between the two polypeptides.

Figures 8 shows the regions of identity between the amino acid sequence of the BM-HABP protein (SEQ ID NO:11) and the translation product of the TSG-6 protein from Mus musculus (See Genbank Accession No. 2062475), as determined by Megalign (DNA Star suite of programs) analysis. Identical amino acids between the two polypeptides are shaded, while the non-identical regions remain unshaded. By examining the regions of amino acids shaded and/or unshaded, the skilled artisan can readily identify conserved domains between the two polypeptides.

Figure 9 shows a structural analysis of the full-length WF-HABP amino acid sequence of Figures 1A-H (SEQ ID NO:2), generated using the default parameters of the recited computer programs. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probabilities are shown. In the "Antigenic Index - Jameson-Wolf" graph, amino acid residues: M-1 to I-9 as depicted in Figures 1A-H (SEQ ID NO:2) correspond to the shown highly antigenic regions of WF-HABP protein.

Figure 10 shows a structural analysis of WF-HABP partial amino acid sequence of Figures 2A-B (SEQ ID NO:5), generated using the default parameters of the recited computer programs. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probabilities are shown. In the "Antigenic Index - Jameson-Wolf" graph, amino acid residues: M-1 to I-9 as depicted in Figures 2A-B (SEQ ID NO:5) correspond to the shown highly antigenic regions of WF-HABP protein.

Figure 11 shows a structural analysis of OE-HABP partial amino acid sequence of Figures 2A-B (SEQ ID NO:8), generated using the default parameters of the recited computer programs. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probabilities are shown. In the "Antigenic Index - Jameson-Wolf" graph, amino acid residues: M-1 to I-9 as depicted in Figures 3A-B (SEQ ID NO:8) correspond to the shown highly antigenic regions of OE-HABP protein.

Figure 12 shows a structural analysis of BM-HABP partial amino acid sequence of Figures 4A-B (SEQ ID NO:11), generated using the default parameters of the recited computer programs. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probabilities are shown. In the "Antigenic Index - Jameson-Wolf" graph, amino acid residues: M-1 to I-9 as depicted in Figures 4A-B (SEQ ID NO:11) correspond to the shown highly antigenic regions of BM-HABP protein.

#### Detailed Description of the Invention

*Summary* The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding a full-length WF-HABP polypeptide (Figures 1A-H (SEQ ID NO:1)). The full-length WF-HABP protein shown in Figures 1A-H shares sequence homology with the human TSG-6 protein (Figures 5A-G (SEQ ID NO:3)).

The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding a WF-HABP polypeptide (Figures 2A-B (SEQ ID NO:6)), the amino acid sequence of which was determined by sequencing a cloned cDNA (Clone HWFBG79). The WF-HABP protein shown in Figures 2A-B shares sequence homology with human cartilage link protein (Figures 6 (SEQ ID NO:6)). The nucleotide sequence shown in Figures 2A-B (SEQ ID NO:4) was obtained by sequencing a cDNA clone (Clone HWFBG79). On December 1, 1998, the plasmid corresponding to this clone was deposited with the American Type Culture Collection, 10801 University Blvd, Manassas, Virginia, 20110-2209, and was assigned accession number 203503. The deposited cDNA is contained in the pBluescript plasmid (Stratagene, La Jolla, CA).

The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding a OE-HABP polypeptide (Figures 3A-B (SEQ ID NO:8)), the amino acid sequence of which was determined by sequencing a cloned cDNA (Clone HOEDH76). The OE-HABP protein shown in Figures 3A-B (SEQ ID NO:8) shares sequence homology with the Gallus gallus cartilage link protein (Figures 7 (SEQ ID NO:9)). The nucleotide sequence shown in Figures 3A-B (SEQ December 1, 1998, the

plasmid corresponding to this clone was deposited with the American Type Culture Collection, 10801 University Blvd, Manassas, Virginia, 20110-2209, and was assigned accession number 203501. The deposited cDNA is contained in the pBluescript plasmid (Stratagene, La Jolla, CA).

5 The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding a BM-HABP polypeptide (Figures 4A-B (SEQ ID NO:11)), the amino acid sequence of which was determined by sequencing a cloned cDNA (Clone HBMVC21). The BM-HABP protein shown in Figures 4A-B shares sequence homology with the *Mus musculus* TSG-6 protein (Figures 8 (SEQ ID NO:11)). The  
10 nucleotide sequence shown in Figures 4A-B (SEQ ID NO:10) was obtained by sequencing a cDNA clone (Clone HBMVC21). On December 1, 1998, the plasmid corresponding to this clone was deposited with the American Type Culture Collection, 10801 University Blvd, Manassas, Virginia, 20110-2209, and was assigned accession number 203502. The deposited cDNA is contained in the pBluescript plasmid  
15 (Stratagene, La Jolla, CA).

As used herein, "full-length WF-HABP protein", "full-length WF-HABP receptor", "full-length receptor protein", "full-length WF-HABP", and "full-length WF-HABP polypeptide" refer to all polypeptides resulting from the alternate splicing of the genomic DNA sequences encoding proteins having regions of amino acid sequence identity and HA binding activity which correspond to the protein shown in Figures 1A-H (SEQ ID NO:2). The full-length WF-HABP protein shown in Figures 1A-H is an example of such a receptor protein.

As used herein, "WF-HABP protein", "WF-HABP fragments", "WF-HABP", partial WF-HABP", "WF-HABP", and "WF-HABP polypeptide" refer to all polypeptides resulting from the alternate splicing of the genomic DNA sequences encoding proteins having regions of amino acid sequence identity and HA binding activity which correspond to the protein shown in Figures 2A-B (SEQ ID NO:5). The WF-HABP protein shown in Figures 2A-B is an example of such a protein.

As used herein, "OE-HABP protein", "OE-HABP fragments", "partial OE-HABP", "OE-HABP", and "OE-HABP polypeptide" refer to all polypeptides resulting from the alternate splicing of the genomic DNA sequences encoding proteins having regions of amino acid sequence identity and HA binding activity which correspond to the protein shown in Figures 3A-B (SEQ ID NO:8). The OE-HABP protein shown in Figures 3A-B is an example of such a protein.

35 As used herein, "BM-HABP protein", "BM-HABP fragments", "partial BM-HABP", "BM-HABP", and "BM-HABP polypeptide" refer to all polypeptides resulting from the alternate splicing of the genomic DNA sequences encoding proteins having

regions of amino acid sequence identity and HA binding activity which correspond to the protein shown in Figures 4A-B (SEQ ID NO:11). The BM-HABP protein shown in Figures 4A-B is an example of such a protein.

## 5 Nucleic Acid Molecules

Using the information provided herein, such as the nucleotide sequence in Figures 1A-B (SEQ ID NO:1), nucleic acid molecules of the present invention encoding the full-length WF-HABP polypeptides may be obtained using standard cloning and screening procedures, such as those used for cloning cDNAs using mRNA as starting material. Northern analysis has revealed expression of the full-length WF-HABP transcript in a variety of tissues. The highest level of expression was observed in the heart, placenta and lung, with next highest levels found in the liver, pancreas, and skeletal muscle, and lower expression found in the brain and kidney. Four major transcripts of 9.5, 4.5, 3.0 and 2.4 Kb were detected. The 9.5 Kb band appeared to be the predominant mRNA and was especially prominent in the placenta and the heart.

The expression pattern of the full-length WF-HABP was also examined in human smooth muscle cells (SMCs), human fetal lung fibroblasts (ETL), human umbilical vein endothelial cells (HUVECs), as well as in HL-60 and U937 cells. Full-length WF-HABP mRNA expression was not detected in either uninduced or TPA-stimulated HL-60 cells. A minor 2.4 Kb band was detected in all of the other cell types examined. Induction of U937 cells with TPA resulted in a slight decrease of the signal. However, it is noteworthy that full-length WF-HABP mRNAs of 9.5, 4.5 and 3.0 Kb were expressed exclusively by HUVECs.

Thus, any of these tissues or cell types provide a source of full-length WF-HABP mRNA. Additionally, any tissue or cell source may be utilized to routinely clone full-length WF-HABP genomic DNA using techniques known in the art. Illustrative of the invention, the nucleic acid molecule described in Figures 1A-H (SEQ ID NO:1) was discovered in a cDNA library derived from white fat tissue.

Using the information provided herein, such as the nucleotide sequence in Figures 2A-B (SEQ ID NO:4), nucleic acid molecules of the present invention encoding the WF-HABP polypeptides may be obtained using standard cloning and screening procedures, such as those used for cloning cDNAs using mRNA as starting material. Northern analysis has revealed expression of the WF-HABP transcript in a variety of tissues. The highest level of expression was observed in the heart, placenta and lung, with next highest levels found in the liver, pancreas, and skeletal muscle, and lower expression found in the brain and kidney. Four major transcripts of 9.5, 4.5, 3.0 and

2.4 Kb were detected. The 9.5 Kb band appeared to be the predominant mRNA and was especially prominent in the placenta and the heart.

The expression pattern of WF-HABP was also examined in human smooth muscle cells (SMCs), human fetal lung fibroblasts (ETL), human umbilical vein endothelial cells (HUVECs), as well as in HL-60 and U937 cells. WF-HABP mRNA expression was not detected in either uninduced or TPA-stimulated HL-60 cells. A minor 2.4 Kb band was detected in all of the other cell types examined. Induction of U937 cells with TPA resulted in a slight decrease of the signal. However, it is noteworthy that WF-HABP mRNAs of 9.5, 4.5 and 3.0 Kb were expressed exclusively by HUVECs.

Thus, any of these tissues or cell types provide a source of WF-HABP mRNA. Additionally, any tissue or cell source may be utilized to routinely clone WF-HABP genomic DNA using techniques known in the art. Illustrative of the invention, the nucleic acid molecule described in Figures 2A-B (SEQ ID NO:4) was discovered in a cDNA library derived from white fat tissue.

Using the information provided herein, such as the nucleotide sequence in Figures 3A-B (SEQ ID NO:7), nucleic acid molecules of the present invention encoding the OE-HABP polypeptides may be obtained using standard cloning and screening procedures, such as those used for cloning cDNAs using mRNA as starting material. Northern analysis has revealed expression of the OE-HABP transcript in a variety of tissues. The highest level of OE-HABP mRNA expression was detected in lung, placenta, and heart, with highest expression observed in the lung as a 2.2 Kb transcript. The expression pattern of OE-HABP was also examined in human smooth muscle cells (SMCs), human fetal lung fibroblasts (ETL), human umbilical vein endothelial cells (HUVECs), as well as in HL-60 and U937 cells. The 2.2 Kb OE-HABP transcript identified supra was expressed by both HUVECs and SMCs, but not by ETL, HL60 or U937 cells. Interestingly, U937 cells responded to stimulation with TPA by expressing a major new 4.3 Kb transcript and minor bands of 3.8, and 3 Kb.

Thus, any of these tissues or cell types provide a source of OE-HABP mRNA. Additionally, any tissue or cell source may be utilized to routinely clone OE-HABP genomic DNA using techniques known in the art. Illustrative of the invention, the nucleic acid molecule described in Figures 3A-B (SEQ ID NO:7) was discovered in a cDNA library derived from osteoblast tissue.

Using the information provided herein, such as the nucleotide sequence in Figures 4A-B (SEQ ID NO:10), nucleic acid molecules of the present invention encoding the BM-HABP polypeptides may be obtained using standard cloning and screening procedures, such as those used for cloning cDNAs using mRNA as starting

material. Northern analysis has revealed expression of the BM-HABP transcript in a variety of tissues. The highest level of BM-HABP mRNA expression was apparent only in the liver and appeared as a smear between 5 and 2 Kb. The expression of BM-HABP was also analyzed in human fetal brain, lung, liver and kidney and found that a distinct 9.5 Kb mRNA was expressed at an elevated level in fetal liver with a low level of signal also observed the lung.

The expression pattern of OE-HABP was also examined in human smooth muscle cells (SMCs), human fetal lung fibroblasts (ETL), human umbilical vein endothelial cells (HUVECs), as well as in HL-60 and U937 cells. There was no detectable mRNA expression of BM-HABP in any of the above cell lines.

Thus, any of these tissues or cell types provide a source of BM-HABP mRNA. Additionally, any tissue or cell source may be utilized to routinely clone BM-HABP genomic DNA using techniques known in the art. Illustrative of the invention, the nucleic acid molecule described in Figures 4A-B (SEQ ID NO:10) was discovered in a cDNA library derived from bone marrow tissue.

~~Sub~~ The determined nucleotide sequence of the full-length WF-HABP cDNA of Figures 1A-H (SEQ ID NO:1) contains an open reading frame encoding a polytopic polypeptide of about 2100 amino acid residues, with a HA-binding domain, EGF-like Type 1 domains, EGF-like Type 2 domains; laminin-type EGF domains; link protein domain; cytochrome P450 cysteine heme-iron ligand binding domains; a prokaryotic membrane lipoprotein lipid attachment site domains, and having a deduced molecular weight of about 231445.37 Da. The WF-HABP protein shown in Figures 1A-H (SEQ ID NO:1) is predicted to contain domains which are about 48% identical to the human hyaluronan binding protein TSG-6 protein depicted in SEQ ID NO:6 (see Figures 6A-B) using the computer program "MegAlign" (DNASTAR suite of software programs). In addition to having homology, TSG-6 and the full-length WF-HABP are thought to share the same topological structure based upon their intrinsic hyaluronan binding activity. For example, like TSG-6, the full-length WF-HABP contains a hyaluronan binding domain. As discussed above, TSG-6 has been shown to be a hyaluronan binding protein and play a vital role in arthritis, anti-inflammatory activity, and the vascular injury response.

The determined nucleotide sequence of the WF-HABP cDNA of Figures 2A-B (SEQ ID NO:4) contains an open reading frame encoding a polytopic polypeptide of about 457 amino acid residues, with a HA-binding domain, an EGF-like Type 2 domain, and a link protein domain, and having a deduced molecular weight of about 48448.90 Da. The WF-HABP protein shown in Figures 2A-B (SEQ ID NO:2) is predicted to be about 48% identical to the human hyaluronan binding protein TSG-6

protein depicted in SEQ ID NO:6 (see Figures 6A-B) using the computer program "MegAlign" (DNASTar suite of software programs). In addition to having homology, TSG-6 and WF-HABP are thought to share the same topological structure based upon their intrinsic hyaluronan binding activity. For example, like TSG-6, WF-HABP contains a hyaluronan binding domain. As discussed above, TSG-6 has been shown to be a hyaluronan binding protein and play a vital role in arthritis, anti-inflammatory activity, and the vascular injury response.

The determined nucleotide sequence of the OE-HABP cDNA of Figures 3A-B (SEQ ID NO:7) contains an open reading frame encoding a polytopic polypeptide of about 289 amino acid residues, with a HA-binding domain, 6 transmembrane domains, 4 extracellular domains, and a pore loop, and having a deduced molecular weight of about 33174.55 Da. The OE-HABP protein shown in Figures 3A-B (SEQ ID NO:8) is predicted to be about 49% identical to the collagen link protein depicted in SEQ ID NO:9 (see Figures 7A-B) using the computer program "MegAlign" (DNASTar suite of software programs). In addition to having homology, collagen link protein and WF-HABP are thought to share the same topological structure based upon their intrinsic hyaluronan binding activity. For example, like collagen link protein, WF-HABP contains a hyaluronan binding domain. As discussed above, collagen link protein has been shown to be a hyaluronan binding protein and play a vital role in arthritis, anti-inflammatory activity, and the vascular injury response.

The determined nucleotide sequence of the BM-HABP cDNA of Figures 4A-B (SEQ ID NO:8)<sup>10</sup> contains an open reading frame encoding a polytopic polypeptide of about 353 amino acid residues, with a HA-binding domain, 6 transmembrane domains, 4 extracellular domains, and a pore loop, and having a deduced molecular weight of about 36063.32 Da. The OE-HABP protein shown in Figures 4A-B (SEQ ID NO:10) is predicted to be about 43% identical to the TSG-6 protein depicted in SEQ ID NO:11 (see Figures 8A-B) using the computer program "MegAlign" (DNASTar suite of software programs). In addition to having homology, the TSG-6 protein and WF-HABP are thought to share the same topological structure based upon their intrinsic hyaluronan binding activity. For example, like the TSG-6 protein, WF-HABP contains a hyaluronan binding domain. As discussed above, TSG-6 protein has been shown to be a hyaluronan binding protein and play a vital role in arthritis, anti-inflammatory activity, and the vascular injury response.

Nucleic acid molecules of the present full-length WF-HABP invention may be in the form of RNA, such as mRNA, or in the form of DNA, including, for instance, cDNA and genomic DNA obtained by cloning or produced synthetically. The DNA may be double-stranded or single-stranded. Single-stranded DNA or RNA may be the

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coding strand, also known as the sense strand, or it may be the non-coding strand, also referred to as the anti-sense strand or complementary strand.

Nucleic acid molecules of the present WF-HABP invention may be in the form of RNA, such as mRNA, or in the form of DNA, including, for instance, cDNA and genomic DNA obtained by cloning or produced synthetically. The DNA may be double-stranded or single-stranded. Single-stranded DNA or RNA may be the coding strand, also known as the sense strand, or it may be the non-coding strand, also referred to as the anti-sense strand or complementary strand.

Nucleic acid molecules of the present OE-HABP invention may be in the form of RNA, such as mRNA, or in the form of DNA, including, for instance, cDNA and genomic DNA obtained by cloning or produced synthetically. The DNA may be double-stranded or single-stranded. Single-stranded DNA or RNA may be the coding strand, also known as the sense strand, or it may be the non-coding strand, also referred to as the anti-sense strand or complementary strand.

Nucleic acid molecules of the present BM-HABP invention may be in the form of RNA, such as mRNA, or in the form of DNA, including, for instance, cDNA and genomic DNA obtained by cloning or produced synthetically. The DNA may be double-stranded or single-stranded. Single-stranded DNA or RNA may be the coding strand, also known as the sense strand, or it may be the non-coding strand, also referred to as the anti-sense strand or complementary strand.

By "isolated" nucleic acid molecule(s) is intended a nucleic acid molecule, DNA or RNA, which has been removed from its native environment. For example, recombinant DNA molecules contained in a vector are considered isolated for the purposes of the present invention. Isolated RNA molecules include *in vivo* or *in vitro* RNA transcripts of the DNA molecules of the present invention. Further examples of isolated DNA molecules include recombinant DNA molecules maintained in heterologous host cells or purified (partially or substantially) DNA molecules in solution. However, a nucleic acid contained in a clone that is a member of a library (e.g., a genomic or cDNA library) that has not been isolated from other members of the library (e.g., in the form of a homogeneous solution containing the clone and other members of the library) or which is contained on a chromosome preparation (e.g., a chromosome spread), is not "isolated" for the purposes of this invention. Isolated nucleic acid molecules according to the present invention may be produced naturally, recombinantly, or synthetically.

In one embodiment, nucleic acid molecules of the present invention include DNA molecules comprising an open reading frame (ORF) shown in Figures 1A-H (SEQ ID NO:1); and DNA molecules which comprise a sequence substantially different

from those described above, but which, due to the degeneracy of the genetic code, still encode the full-length WF-HABP polypeptide shown in Figures 1A-H (SEQ ID NO:1). Of course, the genetic code is well known in the art. Thus, it would be routine for one skilled in the art to generate such degenerate variants.

5 In one embodiment, nucleic acid molecules of the present invention include DNA molecules comprising an open reading frame (ORF) shown in Figures 2A-B (SEQ ID NO:4); and DNA molecules which comprise a sequence substantially different from those described above, but which, due to the degeneracy of the genetic code, still encode WF-HABP polypeptide shown in Figures 2A-B (SEQ ID NO:4). Of course,  
10 the genetic code is well known in the art. Thus, it would be routine for one skilled in the art to generate such degenerate variants.

In one embodiment, nucleic acid molecules of the present invention include DNA molecules comprising an open reading frame (ORF) shown in Figures 3A-B (SEQ ID NO:8); and DNA molecules which comprise a sequence substantially different  
15 from those described above, but which, due to the degeneracy of the genetic code, still encode OE-HABP polypeptide shown in Figures 3A-B (SEQ ID NO:8). Of course, the genetic code is well known in the art. Thus, it would be routine for one skilled in the art to generate such degenerate variants.

In one embodiment, nucleic acid molecules of the present invention include  
20 DNA molecules comprising an open reading frame (ORF) shown in Figures 4A-B (SEQ ID NO:11); and DNA molecules which comprise a sequence substantially different from those described above, but which, due to the degeneracy of the genetic code, still encode BM-HABP polypeptide shown in Figures 4A-B (SEQ ID NO:11). Of course, the genetic code is well known in the art. Thus, it would be routine for one  
25 skilled in the art to generate such degenerate variants.

In another embodiment, the invention provides isolated nucleic acid molecules encoding the full-length WF-HABP polypeptide having the amino acid sequence. In a further embodiment, these nucleic acid molecules encode the full-length polypeptide lacking the N-terminal methionine (amino acid residues 2 to 2100 of SEQ ID NO:2).  
30 The invention further provides isolated nucleic acid molecules having the nucleotide sequences shown in Figures 1A-H (SEQ ID NO:1), the nucleotide sequence of the cDNA contained in the above-described deposited clone (clone HWFBG79); or nucleic acid molecules having a sequence complementary to one of the above sequences. Such isolated molecules, particularly DNA molecules, have uses that include, but are not  
35 limited to, probes for gene mapping by *in situ* hybridization with chromosomes, and for detecting expression of the full-length WF-HABP genes of the present invention in human tissue, for instance, by Northern blot analysis.

In another embodiment, the invention provides isolated nucleic acid molecules encoding the WF-HABP polypeptide having the amino acid sequence encoded by the cDNA clone contained in the plasmid deposited as ATCC Deposit No. 203503 on December 1, 1998. In a further embodiment, these nucleic acid molecules encode the

5 full-length polypeptide lacking the N-terminal methionine (amino acid residues 2 to 457 of SEQ ID NO:5). The invention further provides isolated nucleic acid molecules having the nucleotide sequences shown in Figures 2A-B (SEQ ID NO:4), the nucleotide sequence of the cDNA contained in the above-described deposited clone (clone HWFBG79); or nucleic acid molecules having a sequence complementary to one of the

10 above sequences. Such isolated molecules, particularly DNA molecules, have uses that include, but are not limited to, probes for gene mapping by *in situ* hybridization with chromosomes, and for detecting expression of the WF-HABP genes of the present invention in human tissue, for instance, by Northern blot analysis.

In another embodiment, the invention provides isolated nucleic acid molecules

15 encoding the OE-HABP polypeptide having the amino acid sequence encoded by the cDNA clone contained in the plasmid deposited as ATCC Deposit No. 203501 on December 1, 1998. In a further embodiment, these nucleic acid molecules encode the full-length polypeptide lacking the N-terminal methionine (amino acid residues 2 to 289 of SEQ ID NO:8). The invention further provides isolated nucleic acid molecules

20 having the nucleotide sequences shown in Figures 3A-B (SEQ ID NO:7), the nucleotide sequence of the cDNA contained in the above-described deposited clone (clone HOEDH76); or nucleic acid molecules having a sequence complementary to one of the above sequences. Such isolated molecules, particularly DNA molecules, have uses that include, but are not limited to, probes for gene mapping by *in situ* hybridization with

25 chromosomes, and for detecting expression of the OE-HABP genes of the present invention in human tissue, for instance, by Northern blot analysis.

In another embodiment, the invention provides isolated nucleic acid molecules encoding the BM-HABP polypeptide having the amino acid sequence encoded by the cDNA clone contained in the plasmid deposited as ATCC Deposit No. 203502 on

30 December 1, 1998. In a further embodiment, these nucleic acid molecules encode the full-length polypeptide lacking the N-terminal methionine (amino acid residues 2 to 353 of SEQ ID NO:11). The invention further provides isolated nucleic acid molecules having the nucleotide sequences shown in Figures 4A-B (SEQ ID NO:10), the nucleotide sequence of the cDNA contained in the above-described deposited clone

35 (clone HB MVC21); or nucleic acid molecules having a sequence complementary to one of the above sequences. Such isolated molecules, particularly DNA molecules, have uses that include, but are not limited to, probes for gene mapping by *in situ*

hybridization with chromosomes, and for detecting expression of the BM-HABP genes of the present invention in human tissue, for instance, by Northern blot analysis.

The present invention is further directed to fragments of the isolated nucleic acid molecules (i.e. polynucleotides) described herein. By a fragment of an isolated nucleic acid molecule having, for example, a nucleotide sequence encoding the polypeptide sequence depicted in Figures 1A-H (SEQ ID NO:2), the nucleotide sequence shown in Figures 1A-H (SEQ ID NO:1), or the complementary strand thereto, is intended fragments at least 15 nt, and more preferably at least 20 nt, still more preferably at least 30 nt, and even more preferably, at least 40, 50, 100, 150, 200, 250, 300, 325, 350, 375, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150, 1200, 1250, 1300, 1350, 1400, 1450, 1500, 1550, 1600, 1650, 1700, 1750, 1800, 1850, 1900, 1950, 2000, 2050, 2100, 2150, 2200, 2250, 2300, 2350, 2400, 2450, 2500, 2550, 2600, 2650, 2700, 2750, 2800, 2850, 2900, 2950, 3000, 3050, 3100, 3150, 3200, 3250, 3300, 3350, 3400, 3450, 3500, 3550, 3600, 3650, 3700, 3750, 3800, 3850, 3900, 3950, 4000, 4050, 4100, 4150, 4200, 4250, 4300, 4350, 4400, 4450, 4500, 4550, 4600, 4650, 4700, 4750, 4800, 4850, 4900, 4950, 5000, 5050, 5100, 5150, 5200, 5250, 5300, 5350, 5400, 5450, 5500, 5550, 5600, 5650, 5700, 5750, 5800, 5850, 5900, 5950, 6000, 6050, 6100, 6150, 6200, 6250, 6300, 6350, 6400, 6450, 6500, 6550, 6600, 6650, 6700, 6750 or 6777 nt in length. These fragments have numerous uses which include, but are not limited to, diagnostic probes and primers as discussed herein. Of course, larger fragments, are also useful according to the present invention as are fragments corresponding to most, if not all, of the nucleotide sequences as shown in Figures 1A-H (SEQ ID NO:1). By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from, for example, the nucleotide sequence of the deposited cDNA, or the nucleotide sequence as shown in Figures 1A-H (SEQ ID NO:1).

The present invention is further directed to fragments of the isolated nucleic acid molecules (i.e. polynucleotides) described herein. By a fragment of an isolated nucleic acid molecule having, for example, the nucleotide sequence of the deposited cDNA (clone HWFBG79), a nucleotide sequence encoding the polypeptide sequence encoded by the deposited cDNA, a nucleotide sequence encoding the polypeptide sequence depicted in Figures 2A-B (SEQ ID NO:5), the nucleotide sequence shown in Figures 2A-B (SEQ ID NO:4), or the complementary strand thereto, is intended fragments at least 15 nt, and more preferably at least 20 nt, still more preferably at least 30 nt, and even more preferably, at least 40, 50, 100, 150, 200, 250, 300, 325, 350, 375, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150, 1200, 1250, 1300, 1350, 1400, 1450, 1500, or 1522 nt in length. These fragments

have numerous uses which include, but are not limited to, diagnostic probes and primers as discussed herein. Of course, larger fragments are also useful according to the present invention as are fragments corresponding to most, if not all, of the nucleotide sequences of the deposited cDNA (clone HWFBG79) or as shown in  
 5 Figures 2A-B (SEQ ID NO:4). By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from, for example, the nucleotide sequence of the deposited cDNA, or the nucleotide sequence as shown in Figures 2A-B (SEQ ID NO:4).

The present invention is further directed to fragments of the isolated nucleic acid  
 10 molecules (i.e. polynucleotides) described herein. By a fragment of an isolated nucleic acid molecule having, for example, the nucleotide sequence of the deposited cDNA (clone HOEDH76), a nucleotide sequence encoding the polypeptide sequence encoded by the deposited cDNA, a nucleotide sequence encoding the polypeptide sequence depicted in Figures 3A-B (SEQ ID NO:7), the nucleotide sequence shown in Figures  
 15 3A-B (SEQ ID NO:7), or the complementary strand thereto, is intended fragments at least 15 nt, and more preferably at least 20 nt, still more preferably at least 30 nt, and even more preferably, at least 40, 50, 100, 150, 200, 250, 300, 325, 350, 375, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 985 nt in length. These fragments have numerous uses which include, but are not limited to, diagnostic probes and primers as discussed herein. Of course, larger fragments are also useful according to the present invention as are fragments corresponding to most, if not all, of the nucleotide sequences of the deposited cDNA (clone HOEDH76) or as shown in Figures 3A-B (SEQ ID NO:7). By a fragment at least 20 nt in length, for example, is intended  
 20 fragments which include 20 or more contiguous bases from, for example, the nucleotide sequence of the deposited cDNA, or the nucleotide sequence as shown in Figures 3A-B (SEQ ID NO:7).  
 25

The present invention is further directed to fragments of the isolated nucleic acid molecules (i.e. polynucleotides) described herein. By a fragment of an isolated nucleic acid molecule having, for example, the nucleotide sequence of the deposited cDNA  
 30 (clone HBMVC21), a nucleotide sequence encoding the polypeptide sequence encoded by the deposited cDNA, a nucleotide sequence encoding the polypeptide sequence depicted in Figures 4A-B (SEQ ID NO:10), the nucleotide sequence shown in Figures 4A-B (SEQ ID NO:10), or the complementary strand thereto, is intended fragments at least 15 nt, and more preferably at least 20 nt, still more preferably at least 30 nt, and  
 35 even more preferably, at least 40, 50, 100, 150, 200, 250, 300, 325, 350, 375, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150, 1200, 1250, or 1259 nt in length. These fragments have numerous uses which include,

but are not limited to, diagnostic probes and primers as discussed herein. Of course, larger fragments are also useful according to the present invention as are fragments corresponding to most, if not all, of the nucleotide sequences of the deposited cDNA (clone HBMVC21) or as shown in Figures 4A-B (SEQ ID NO:10). By a fragment at  
 5 least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from, for example, the nucleotide sequence of the deposited cDNA, or the nucleotide sequence as shown in Figures 4A-B (SEQ ID NO:10).

Representative examples of the full-length WF-HABP polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist  
 10 of, a sequence from nucleotide 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, 251 to 300, 301 to 350, 351 to 400, 401 to 450, 451 to 500, 501 to 550, 551 to 600, 600 to 650, 651 to 700, 701 to 750, 751 to 800, 800 to 850, 851 to 900, 901 to 950, 951 to 1000, 1001 to 1050, 1051 to 1100, 1101 to 1150, 1151 to 1200, 1201 to 1250,  
 15 1251 to 1300, 1301 to 1350, 1351 to 1400, 1401 to 1450, 1451 to 1500, 1501 to 1550, 1551 to 1600, 1601 to 1650, 1651 to 1700, 1701 to 1750, 1751 to 1800, 1801 to 1850, 1851 to 1900, 1901 to 1950, 1951 to 2000, 2001 to 2050, 2051 to 2100, 2101 to 2150, 2151 to 2200, 2201 to 2250, 2251 to 2300, 2301 to 2350, 2351 to 2400, 2401 to 2450, 2451 to 2500, 2501 to 2550, 2551 to 2600, 2601 to 2650, 2651 to 2700, 2701 to 2750, 2751 to 2800, 2801 to 2850, 2900, 2901 to 2950, 2951 to  
 20 3000, 3001 to 3050, 3051 to 3100, 3101 to 3150, 3151 to 3200, 3201 to 3250, 3251 to 3300, 3301 to 3350, 3351 to 3400, 3401 to 3450, 3451 to 3500, 3501 to 3550, 3551 to 3600, 3601 to 3650, 3651 to 3700, 3701 to 3750, 3751 to 3800, 3801 to 3850, 3851 to 3900, 3901 to 3950, 4000, 4001 to 4050, 4051 to 4100, 4101 to 4150, 4151 to 4200, 4201 to 4250, 4251 to 4300, 4301 to 4350, 4351 to 4400, 4401 to  
 25 4450, 4451 to 4500, 4501 to 4550, 4551 to 4600, 4601 to 4650, 4651 to 4700, 4701 to 4750, 4751 to 4800, 4801 to 4850, 4851 to 4900, 4901 to 4950, 4951 to 5000, 5001 to 5050, 5051 to 5100, 5101 to 5150, 5151 to 5200, 5201 to 5250, 5251 to 5300, 5301 to 5350, 5351 to 5400, 5401 to 5450, 5451 to 5500, 5501 to 5550, 5551 to 5600, 5601, 5650, 5652 to 5700, 5701 to 5750, 5751 to 5800, 5801 to 5850, 5851  
 30 to 5900, 5901 to 5950, 5951 to 6000, 6050, 6051 to 6100, 6101 to 6150, 6151 to 6200, 6201 to 6250, 6251 to 6300, 6301 to 6350, 6351 to 6400, 6401 to 6450, 6451 to 6500, 6501 to 6550, 6551 to 6600, 6601 to 6650, 6651 to 6700, 6701 to 6750, 6751 to 6777 of SEQ ID NO:1, or the complementary strand thereto. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2,  
 35 or 1) nucleotides, at either terminus or at both termini.

Representative examples of WF-HABP polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a

sequence from nucleotide 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, 251 to 300, 301 to 350, 351 to 400, 401 to 450, 451 to 500, 501 to 550, 551 to 600, 600 to 650, 651 to 700, 701 to 750, 751 to 800, 800 to 850, 851 to 900, 901 to 950, 951 to 1000, 1001 to 1050, 1051 to 1100, 1101 to 1150, 1151 to 1200, 1201 to 1250, 1251 to 1300, 1301 to 1350, 1351 to 1400, 1401 to 1450, 1451 to 1500, and/or 1501 to 1522, of SEQ ID NO:4, or the complementary strand thereto, or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

Representative examples of OE-HABP polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from nucleotide 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, 251 to 300, 301 to 350, 351 to 400, 401 to 450, 451 to 500, 501 to 550, 551 to 600, 600 to 650, 651 to 700, 701 to 750, 751 to 800, 800 to 850, 851 to 900, 901 to 950, and/or 951 to 985, of SEQ ID NO:7, or the complementary strand thereto, or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

Representative examples of BM-HABP polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from nucleotide 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, 251 to 300, 301 to 350, 351 to 400, 401 to 450, 451 to 500, 501 to 550, 551 to 600, 600 to 650, 651 to 700, 701 to 750, 751 to 800, 800 to 850, 851 to 900, 901 to 950, 951 to 1000, 1001 to 1050, 1051 to 1100, 1101 to 1150, 1151 to 1200, 1201 to 1250, and/or 1251 to 1259 of SEQ ID NO:10, or the complementary strand thereto, or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

In specific embodiments, the polynucleotide fragments of the full-length WF-HABP invention comprise, or alternatively, consist of, a sequence from nucleotide 1262 to 4595, 4595 to 5552, 1220 to 1262, 1262 to 1300, 1301 to 1340, 1341 to 1380, 1381 to 1420, 1421 to 1460, 1461 to 1500, 1501 to 1540, 1541 to 1580, 1581 to 1620, 1621 to 1660, 1661 to 1700, 1701 to 1740, 1741 to 1780, 1781 to 1820, 1821 to 1860, 1861 to 1900, 1901 to 1940, 1941 to 1980, 1981 to 2020, 2021 to 2040, 2041 to 2080, 2081 to 2120, 2121 to 2160, 2161 to 2200, 2201 to 2240, 2241 to 2280, 2281 to 2320, 2321 to 2360, 2361 to 2400, 2401 to 2440, 2441 to 2480, 2481 to 2520, 2521 to 2560, 2561 to 2600, 2601 to 2640, 2641 to 2680, 2681 to

2720, 2721 to 2760, 2761 to 2800, 2801 to 2840, 2841 to 2880, 2881 to 2920, 2921 to 2960, 2961 to 3000, 3001 to 3040, 3041 to 3080, 3081 to 3120, 3121 to 3160, 3161 to 3200, 3201 to 3240, 3241 to 3280, 3281 to 3320, 3321 to 3360, 3361 to 3400, 3401 to 3440, 3441 to 3480, 3481 to 3520, 3521 to 3560, 3561 to 3600, 3601 to 3640, 3641 to 3680, 3681 to 3720, 3721 to 3760, 3761 to 3800, 3801 to 3840, 3841 to 3880, 3881 to 3920, 3921 to 3960, 3961 to 4000, 4001 to 4040, 4041 to 4080, 4081 to 4120, 4121 to 4160, 4161 to 4200, 4201 to 4240, 4241 to 4280, 4281 to 4320, 4321 to 4360, 4361 to 4400, 4401 to 4440, 4441 to 4480, 4481 to 4520, 4521 to 4560, 4561 to 4600, 4601 to 4640, 4641 to 4680, 4681 to 4720, 4721 to 4760, 4761 to 4800, 4801 to 4840, 4841 to 4880, 4881 to 4920, 4921 to 4960, 4961 to 5000, 5001 to 5040, 5041 to 5080, 5081 to 5120, 5121 to 5160, 5161, 5200, 5201 to 5240, 5241 to 5280, 5281 to 5320, 5321 to 5360, 5361 to 5400, 5401 to 5440, 5441 to 5480, 5481 to 5520, and/or 5521 to 5552, of SEQ ID NO:1 or the complementary strand thereto.

15 In specific embodiments, the polynucleotide fragments of the WF-HABP invention comprise, or alternatively, consist of, a sequence from nucleotide 1 to 688, 1 to 40, 41 to 80, 81 to 120, 121 to 160, 161 to 200, 201 to 240, 241 to 280, 281 to 320, 321 to 380, 381 to 420, 421 to 460, 461 to 500, 501 to 540, 541 to 580, 581 to 620, 621 to 660, 661 to 688, 301 to 612, 350 to 550 of SEQ ID NO:4, or the complementary strand thereto.

20 In specific embodiments, the polynucleotide fragments of the OE-HABP invention comprise, or alternatively, consist of, a sequence from nucleotide 250 to 975, 298 to 453, 746 to 985, 210 to 250, 251 to 290, 291 to 330, 331 to 370, 371 to 410, 411 to 450, 451 to 490, 491 to 530, 531 to 570, 571 to 610, 611 to 650, 651 to 690, 25 691 to 730, 731 to 770, 771 to 810, 811 to 850, 851 to 890, 891 to 930, 931 to 970, and/or 935 to 975 of SEQ ID NO:7, or the complementary strand thereto.

30 In specific embodiments, the polynucleotide fragments of the BM-HABP invention comprise, or alternatively, consist of, a sequence from nucleotide 1 to 458, 806 to 1259, 352 to 663, 1 to 40, 41 to 80, 81 to 120, 121 to 160, 161 to 200, 201 to 240, 241 to 280, 281 to 320, 321 to 380, 381 to 420, 421 to 460, 760 to 805, 806 to 850, 851 to 890, 891 to 930, 931 to 970, 971 to 1010, 1011 to 1050, 1051 to 1090, 1091 to 1130, 1131 to 1170, 1171 to 1210, 1211 to 1250, 1221 to 1259, 311 to 351, 352 to 390, 391 to 430, 431 to 470, 471 to 510, 511 to 550, 551 to 590, 591 to 630, and/or 631 to 663 of SEQ ID NO:10, or the complementary strand thereto.

35 Preferably, the polynucleotide fragments of the invention encode a polypeptide which demonstrates WF-HABP functional activity. By a polypeptide demonstrating "functional activity" is meant, a polypeptide capable of displaying one or more known



functional activities associated with a full-length WF-HABP polypeptide. Such functional activities include, but are not limited to, biological activity (e.g., ion flux, cellular proliferation, cellular migration, cell adhesion), antigenicity [ability to bind (or compete with a full-length WF-HABP polypeptide for binding) to an anti-full-length-WF-HABP antibody], immunogenicity (ability to generate antibody which binds to a full-length WF-HABP polypeptide), and ability to bind to a receptor or ligand for a full-length WF-HABP polypeptide (e.g., hyaluronan, or a chondroitin sulfate proteoglycan).

Preferably, the polynucleotide fragments of the invention encode a polypeptide which demonstrates WF-HABP functional activity. By a polypeptide demonstrating "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a WF-HABP polypeptide. Such functional activities include, but are not limited to, biological activity (e.g., ion flux, cellular proliferation, cellular migration, cell adhesion), antigenicity [ability to bind (or compete with a WF-HABP polypeptide for binding) to an anti-WF-HABP antibody], immunogenicity (ability to generate antibody which binds to a WF-HABP polypeptide), and ability to bind to a receptor or ligand for a WF-HABP polypeptide (e.g., hyaluronan, or a chondroitin sulfate proteoglycan).

Preferably, the polynucleotide fragments of the invention encode a polypeptide which demonstrates OE-HABP functional activity. By a polypeptide demonstrating "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a OE-HABP polypeptide. Such functional activities include, but are not limited to, biological activity (e.g., ion flux, cellular proliferation, cellular migration, cell adhesion), antigenicity [ability to bind (or compete with a OE-HABP polypeptide for binding) to an anti-OE-HABP antibody], immunogenicity (ability to generate antibody which binds to a OE-HABP polypeptide), and ability to bind to a receptor or ligand for a OE-HABP polypeptide (e.g., hyaluronan, or a chondroitin sulfate proteoglycan).

Preferably, the polynucleotide fragments of the invention encode a polypeptide which demonstrates BM-HABP functional activity. By a polypeptide demonstrating "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a BM-HABP polypeptide. Such functional activities include, but are not limited to, biological activity (e.g., ion flux, cellular proliferation, cellular migration, cell adhesion), antigenicity [ability to bind (or compete with a BM-HABP polypeptide for binding) to an anti-BM-HABP antibody], immunogenicity (ability to generate antibody which binds to a BM-HABP polypeptide),

and ability to bind to a receptor or ligand for a BM-HABP polypeptide (e.g., hyaluronan, or a chondroitin sulfate proteoglycan).

Preferred nucleic acid fragments of the invention include nucleic acid molecules encoding one or more full-length WF-HABP receptor domains. In particular

5 embodiments, such nucleic acid fragments comprise, or alternatively consist of, nucleic acid molecules encoding: a polypeptide selected from the group consisting of: (a) an HA binding motif (amino acid residues E-1791 to C-1894 of SEQ ID NO:2); (b) EGF-like Type 1 domains (amino acid residues from C-375 to C-386, amino acid residues from C-943 to C-954, amino acid residues from C-987 to C-998, amino acid residues from

10 C-1582 to C-1593, and amino acid residues from C-1626 to C-1637 of SEQ ID NO:2); (c) EGF-like Type 2 domains (amino acid residues from C-465 to C-478, amino acid residues from C-508 to C-521, amino acid residues from C-551 to C-564, amino acid residues from C-943 to C-957, amino acid residues from C-987 to C-998, amino acid residues from C-1027 to C-1040, amino acid residues from C-1069 to C-1082, amino

15 acid residues from C-1111 to C-1125, amino acid residues from C-1582 to C-1596, amino acid residues from C-1582 to C-1596, amino acid residues from C-1626 to C-1637, amino acid residues from C-1663 to C-1676, amino acid residues from C-1747 to C-1760, and amino acid residues from C-1894 to C-1908 of SEQ ID NO:2); (d) laminin-type EGF domain (amino acid residues from C-943 to C-977, and amino acid

20 residues from C-1582 to C-1616 of SEQ ID NO:2 ); (e) link protein domain (amino acid residues from C-1817 to C-1862 of SEQ ID NO:2); (f) cytochrome P450 cysteine heme-iron ligand binding domains (amino acid residues from F-344 to G-353, and amino acid residues from W-514 to A-523 of SEQ ID NO:2); (g) prokaryotic membrane lipoprotein lipid attachment site domains (amino acid residues from P-1103 to C-1113,

25 and amino acid residues from T-1405 to C-1415 of SEQ ID NO:2; (h) any combination of polypeptides (a)-(g); and (i) the complementary strand of the sense strand encoding any of polypeptides (a)-(h).

Preferred nucleic acid fragments of the invention include nucleic acid molecules encoding one or more WF-HABP receptor domains. In particular embodiments, such

30 nucleic acid fragments comprise, or alternatively consist of, nucleic acid molecules encoding: a polypeptide selected from the group consisting of: (a) an HA binding motif (amino acid residues E-91 to C-194 of SEQ ID NO:4); (b) EGF-like Type 2 domain (amino acid residues C-194 to C-208, of SEQ ID NO:4); (c) a link domain (amino acid residues C-117 to C-162, of SEQ ID NO:4), (d) any combination of polypeptides (a)-(c); and (e) the complementary strand of the sense strand encoding any of polypeptides

35 (a)-(d).

Preferred nucleic acid fragments of the invention include nucleic acid molecules encoding one or more OE-HABP receptor domains. In particular embodiments, such nucleic acid fragments comprise, or alternatively consist of, nucleic acid molecules encoding: a polypeptide selected from the group consisting of: (a) an HA binding motif domain (amino acid residues P-97 to F-168, amino acid residues L-209 to C-286, of SEQ ID NO:7); (b) a link protein domain (amino acid residues C-188 to C-233 of SEQ ID NO:7); (c) any combination of polypeptides (a)-(b); and (d) the complementary strand of the sense strand encoding any of polypeptides (a)-(c).

Preferred nucleic acid fragments of the invention include nucleic acid molecules encoding one or more BM-HABP receptor domains. In particular embodiments, such nucleic acid fragments comprise, or alternatively consist of, nucleic acid molecules encoding: a polypeptide selected from the group consisting of: (a) : an HA binding motif domain (amino acid residues Q-121 to L-215); and (b) the complementary strand of the sense strand encoding polypeptides (a).

The amino acid residues constituting an HA binding motif domain, EGF-like Type 1 domain, EGF-like Type 2 domain, laminin-type EGF domain, a link protein domain, cytochrome P450 cysteine heme-iron ligand binding domains, prokaryotic membrane lipoprotein lipid attachment site domains of the full-length WF-HABP have been predicted by computer analysis and homology determinations (See Figure 1A-H). Thus, as one of ordinary skill would appreciate, the amino acid residues constituting these domains may vary slightly (e.g., by 1 to 15 amino acid residues) depending on the criteria used to define each domain.

The amino acid residues constituting an HA binding motif domain, an EGF-like Type 2 domain, and a link domain of WF-HABP have been predicted by computer analysis and homology determinations (See Figure 2A-B). Thus, as one of ordinary skill would appreciate, the amino acid residues constituting these domains may vary slightly (e.g., by 1 to 15 amino acid residues) depending on the criteria used to define each domain.

The amino acid residues constituting an HA binding motif domain, and a link protein domain, of OE-HABP have been predicted by computer analysis and homology determinations (See Figure 3A-B). Thus, as one of ordinary skill would appreciate, the amino acid residues constituting these domains may vary slightly (e.g., by 1 to 15 amino acid residues) depending on the criteria used to define each domain.

The amino acid residues constituting an HA binding motif domain of BM-HABP have been predicted by computer analysis and homology determinations (See Figure 4A-B). Thus, as one of ordinary skill would appreciate, the amino acid residues

constituting these domains may vary slightly (e.g., by 1 to 15 amino acid residues) depending on the criteria used to define each domain.

Preferred nucleic acid fragments of the invention also include nucleic acid molecules encoding epitope-bearing portions of the full-length WF-HABP. In particular, such nucleic acid fragments of the present invention include nucleic acid molecules encoding: a polypeptide comprising, or alternatively consisting of, amino acid residues: from M-1 to I9, from D-3 to T12, from F-26 to L-35, from I-50 to T-59, from T-54 to W-63, from S-81 to Q-90, from P-117 to P-124, from G-122 to Q-130, from S-152 to F-160, from P-165 to L-173, from D-171 to I-179, from K-207 to L-215, from N-225 to L-234, from P-270 to H-278, from H-272 to I-280, from T-295 to L-303, from D-304 to Y-312, from V-321 to Y-329, from E-336 to F-344, from P-346 to G-354, from C-359 to D-367, from S-366 to A-374, from F-378 to C-386, from S-390 to Q-398, from Q-398 to V-406, from C-410 to G-418, from R-432 to D-440, from M-438 to L-446, from V-457 to C-465, from R-464 to E-472, from G-470 to C-478, from C-484 to C-492, from S-493 to G-501, from G-513 to C-521, from D-525 to G-533, from G-528 to H-536, from G-545 to L-554, from G-556 to C-564, from S-565 to G-573, from C-570 to H-578, from L-602 to A-610, from Q-620 to F-628, from Q-631 to V-639, from L-648 to L-656, from L-653 to V-661, from N-665 to R-673, from W-670 to R-678, from P-707 to G-715, from T-756 to G-764, from S-767 to R-775, from T-788 to N-796, from N-809 to N-816, from L-826 to I-834, from E-853 to N-861, from C-862 to Q-870, from Q-875 to V-883, from S-889 to T-897, from A-899 to C-907, from C-916 to G-924, from G-929 to F-937, from F-937 to C-945, from L-959 to T-967, from Q-978 to S-986, from R-977 to P-1005, from Q-1006 to N-1014, from V-1018 to T-1026, from E-1042 to H-1050, from K-1061 to C-1069, from D-1073 to L-1081, from C-1111 to G-1119, from G-1119 to T-1124, from E-1126 to N-1134, from C-1131 to S-1139, from C-1144 to R-1152, from T-1147 to T-1155, from L-1176 to F-1184, from K-1193 to F-1201, from M-1211 to L-1219, G-1236 to D-1244, from L-1240 to Q-1248, from R-1260 to I-1268, from V-1277 to N-1285, from H-1302 to I-1310, from D-1307 to V-1315, from L-1340 to F-1348, from A-1360 to W-1368, from H-1371 to A-1379, from S-1414 to E-1422, from M-1424 to I-1432, from G-1426 to Q-1434, from P-1453 to D-1461, from F-1463 to N-1471, from P-1480 to E-1488, from Q-1487 to C-1495, from G-1524 to G-1532, from L-1529 to C-1537, from W-1542 to H-1550, from G-1549 to A-1557, from P-1559 to S-1567, from P-1565 to M-1573, from M-1573 to Q-1581, from G-1614 to G-1622, from D-1617 to S-1625, from F-1627 to P-1635, from E-1630 to E-1638, from A-1655 to C-1663, from L-1667 to V-1675, from L-1681 to C-1689, from C-1689 to Q-1697, from L-1707 to W-1715, from C-1717 to D-1725, from D-1725 to E-1733, from

S-1739 to C-1747, from G-1741 to C-1749, from L-1761 to D-1769, from G-1773 to D-1781, from H-1788 to V-1796, from A-1860 to G-1868, from G-1873 to R-1881. K-1876 to A-1884, from A-1893 to V-1901, from S-1906 to D-1914, from N-1734 to F-1942, from D-1944 to Y-1952, from S-1970 to A-1978, from D-1973 to A-1981,  
 5 from N-1987 to D-1995, from S-2005 to S-2013, from L-2085 to G-2093, from Q-2100 to D-2108, from D-2103 to P-2111, from W-2112 to L-2120, from P-2136 to E-2144, from E-2143 to R-2151, from Cys-359 to Gly-363, from Pro-392 to His-395, from Pro-414 to Ser-416, from Pro-487 to Gly-490, from Ser-515 to Asp-517, from Asn-574 to Gly-576, from Pro-708 to Gly-710, from Gln-1006 to Cys-1011, from  
 10 Arg-1114 to Ser-1118, from Cys-1131 to Gly-1137, from Ser-1146 to Gly-1150, from Pro-1305 to Asp-1307, from Pro-1565 to Asp-1568, from Glu-1670 to Gly-1673, from Asp-1684 to Gly-1688, from Pro-1708 to Gly-1714, from Pro-1722 to about Gly-1726, from Asp-2010 to Ser-2013. of SEQ ID NO:2. The inventors have determined that the above polypeptides are antigenic regions of the full-length WF-HABP polypeptide. Methods for determining other such epitope-bearing portions of  
 15 full-length WF-HABP polypeptides are described in detail below.

Preferred nucleic acid fragments of the invention also include nucleic acid molecules encoding epitope-bearing portions of WF-HABP. In particular, such nucleic acid fragments of the present invention include nucleic acid molecules encoding: a  
 20 polypeptide comprising, or alternatively consisting of, amino acid residues: from L-7 to W-15, from C-17 to D-25, from G-26 to H-34, from S-39 to C-47, from L-42 to H-50, from L-61 to D-69, from P-75 to M-83, from H-88 to V-96, from V-159 to V-167, from G-173 to R-181, from N-177 to Y-185, from A-193 to V-201, from T-207 to V-215, from N-234 to F-242, from D-244 to Y-252, from V-259 to M-267, from N-287  
 25 to P-295, from S-305 to S-313, from L-386 to G-394, from D-404 to P-412, from W-413 to L-421, from E-436 to E-444, from and/or from E-445 to I-453 of SEQ ID NO:5. The inventors have determined that the above polypeptides are antigenic regions of the WF-HABP polypeptide. Methods for determining other such epitope-bearing portions of WF-HABP polypeptides are described in detail below.

Preferred nucleic acid fragments of the invention also include nucleic acid molecules encoding epitope-bearing portions of OE-HABP. In particular, such nucleic acid fragments of the present invention include nucleic acid molecules encoding: a  
 30 polypeptide comprising, or alternatively consisting of, amino acid residues: from Y-26 to N-34, from N-37 to N-45, from V-50 to L-58, from L-78 to V-86, from K-90 to E-98, from N-94 to L-102, from L-107 to Y-115, from R-110 to R-118, from V-119 to H-127, from K-125 to I-133, from L-136 to Y-144, from Y-141 to V-148, from D-150  
 35 to L-158, from Y-170 to Q-178. A204 to C-212, from R-230 to L-238, from S-244 to

L-252, from H-249 to V-257, from and/or A-282 to K-289 of SEQ ID NO:8. The inventors have determined that the above polypeptides are antigenic regions of the OE-HABP polypeptide. Methods for determining other such epitope-bearing portions of OE-HABP polypeptides are described in detail below.

5 Preferred nucleic acid fragments of the invention also include nucleic acid molecules encoding epitope-bearing portions of BM-HABP. In particular, such nucleic acid fragments of the present invention include nucleic acid molecules encoding: a polypeptide comprising, or alternatively consisting of, amino acid residues: from T-2 to E-10, from H-7 to Y-15, from G-17 to E-25, from C-22 to D-30, from R-31 to C-39,  
 10 from R-61 to L-69, from T-70 to C-78, from R-75 to H-83, from Y-93 to L-101, from L-107 to P-115, from S-120 to V-128, from Y-133 to E-141, from P-135 to W-143, from Y-148 to T-156, from S-193 to A-201, from S-195 to L-203, from N-220 to T-228, from L-229 to H-237, from L-264 to L-272, from P-271 to C-279, from C-279 to E-287, from A-292 to I-296, from S-301 to A-309, from and/or R-342 to F-350 of  
 15 SEQ ID NO:11. The inventors have determined that the above polypeptides are antigenic regions of the BM-HABP polypeptide. Methods for determining other such epitope-bearing portions of BM-HABP polypeptides are described in detail below.

In another embodiment, the full-length WF-HABP invention provides isolated nucleic acid molecules comprising polynucleotides which hybridize, preferably under  
 20 stringent hybridization conditions, to a portion of one or more of the nucleic acids (i.e., polynucleotides) described herein, such as, for instance, the cDNA clone contained in ATCC Deposit 203503, the polynucleotide sequence depicted in Figures 1A-H (SEQ ID NO:1) or the complementary strand thereto, and/or any of the polynucleotide fragments as described herein. By "stringent hybridization conditions" is intended  
 25 overnight incubation at 42°C in a solution comprising: 50% formamide, 5x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C. By a polynucleotide which hybridizes to a "portion" of a polynucleotide is intended a  
 30 polynucleotide (either DNA or RNA) hybridizing to at least 15 nucleotides (nt), and more preferably at least 20 nt, still more preferably at least 30 nt, and even more preferably 30-70, or 80-150 nt, or the entire length of the reference polynucleotide. By a portion of a polynucleotide of "at least 20 nt in length," for example, is intended 20 or more contiguous nucleotides from the nucleotide sequence of the reference  
 35 polynucleotide (e.g., the complementary strand of the nucleotide sequence shown in Figures 1A-H (SEQ ID NO:1)). Of course, a polynucleotide which hybridizes only to a poly A sequence (such as the 3' terminal poly(A) tail of a cDNA sequence), or to a

complementary stretch of T (or U) residues, would not be included in a polynucleotide of the invention used to hybridize to a portion of a nucleic acid of the invention, since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (i.e., practically any double-stranded cDNA clone generated using oligo dT as a primer). These polynucleotides have uses which include, but are not limited to, diagnostic probes and primers as discussed above and in more detail below.

In another embodiment, the WF-HABP invention provides isolated nucleic acid molecules comprising polynucleotides which hybridize, preferably under stringent hybridization conditions, to a portion of one or more of the nucleic acids (i.e., polynucleotides) described herein, such as, for instance, the cDNA clone contained in ATCC Deposit 203503, the polynucleotide sequence depicted in Figures 2A-B (SEQ ID NO:4) or the complementary strand thereto, and/or any of the polynucleotide fragments as described herein. By "stringent hybridization conditions" is intended overnight incubation at 42°C in a solution comprising: 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C. By a polynucleotide which hybridizes to a "portion" of a polynucleotide is intended a polynucleotide (either DNA or RNA) hybridizing to at least 15 nucleotides (nt), and more preferably at least 20 nt, still more preferably at least 30 nt, and even more preferably 30-70, or 80-150 nt, or the entire length of the reference polynucleotide. By a portion of a polynucleotide of "at least 20 nt in length," for example, is intended 20 or more contiguous nucleotides from the nucleotide sequence of the reference polynucleotide (e.g., the deposited cDNA or the complementary strand of the nucleotide sequence shown in Figures 2A-B (SEQ ID NO:4)). Of course, a polynucleotide which hybridizes only to a poly A sequence (such as the 3' terminal poly(A) tail of a cDNA sequence), or to a complementary stretch of T (or U) residues, would not be included in a polynucleotide of the invention used to hybridize to a portion of a nucleic acid of the invention, since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (i.e., practically any double-stranded cDNA clone generated using oligo dT as a primer). These polynucleotides have uses which include, but are not limited to, diagnostic probes and primers as discussed above and in more detail below.

In another embodiment, the OE-HABP invention provides isolated nucleic acid molecules comprising polynucleotides which hybridize, preferably under stringent hybridization conditions, to a portion of one or more of the nucleic acids (i.e., polynucleotides) described herein, such as, for instance, the cDNA clone contained in

ATCC Deposit 203501, the polynucleotide sequence depicted in Figures 3A-B (SEQ ID NO:7) or the complementary strand thereto, and/or any of the polynucleotide fragments as described herein. By "stringent hybridization conditions" is intended overnight incubation at 42°C in a solution comprising: 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C. By a polynucleotide which hybridizes to a "portion" of a polynucleotide is intended a polynucleotide (either DNA or RNA) hybridizing to at least 15 nucleotides (nt), and more preferably at least 20 nt, still more preferably at least 30 nt, and even more preferably 30-70, or 80-150 nt, or the entire length of the reference polynucleotide. By a portion of a polynucleotide of "at least 20 nt in length," for example, is intended 20 or more contiguous nucleotides from the nucleotide sequence of the reference polynucleotide (e.g., the deposited cDNA or the complementary strand of the nucleotide sequence shown in Figures 3A-B (SEQ ID NO:7)). Of course, a polynucleotide which hybridizes only to a poly A sequence (such as the 3' terminal poly(A) tail of a cDNA sequence), or to a complementary stretch of T (or U) residues, would not be included in a polynucleotide of the invention used to hybridize to a portion of a nucleic acid of the invention, since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (i.e., practically any double-stranded cDNA clone generated using oligo dT as a primer). These polynucleotides have uses which include, but are not limited to, diagnostic probes and primers as discussed above and in more detail below.

In another embodiment, the BM-HABP invention provides isolated nucleic acid molecules comprising polynucleotides which hybridize, preferably under stringent hybridization conditions, to a portion of one or more of the nucleic acids (i.e., polynucleotides) described herein, such as, for instance, the cDNA clone contained in ATCC Deposit 203502, the polynucleotide sequence depicted in Figures 4A-B (SEQ ID NO:10) or the complementary strand thereto, and/or any of the polynucleotide fragments as described herein. By "stringent hybridization conditions" is intended overnight incubation at 42°C in a solution comprising: 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C. By a polynucleotide which hybridizes to a "portion" of a polynucleotide is intended a polynucleotide (either DNA or RNA) hybridizing to at least 15 nucleotides (nt), and more preferably at least 20 nt, still more preferably at least 30 nt, and even more preferably 30-70, or 80-150 nt, or the entire length of the reference polynucleotide. By



a portion of a polynucleotide of "at least 20 nt in length," for example, is intended 20 or more contiguous nucleotides from the nucleotide sequence of the reference polynucleotide (e.g., the deposited cDNA or the complementary strand of the nucleotide sequence shown in Figures 4A-B (SEQ ID NO:10)). Of course, a polynucleotide which hybridizes only to a poly A sequence (such as the 3' terminal poly(A) tail of a cDNA sequence), or to a complementary stretch of T (or U) residues, would not be included in a polynucleotide of the invention used to hybridize to a portion of a nucleic acid of the invention, since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (i.e., practically any double-stranded cDNA clone generated using oligo dT as a primer). These polynucleotides have uses which include, but are not limited to, diagnostic probes and primers as discussed above and in more detail below.

In specific embodiments, the nucleic acid molecules hybridize to the complementary strand of nucleotides 1262 to 4595, 4595 to 5552, 1220 to 1262, 1262 to 1300, 1301 to 1340, 1341 to 1380, 1381 to 1420, 1421 to 1460, 1461 to 1500, 1501 to 1540, 1541 to 1580, 1581 to 1620, 1621 to 1660, 1661 to 1700, 1701 to 1740, 1741 to 1780, 1781 to 1820, 1821 to 1860, 1861 to 1900, 1901 to 1940, 1941 to 1980, 1981 to 2020, 2021 to 2040, 2041 to 2080, 2081 to 2120, 2121 to 2160, 2161 to 2200, 2201 to 2240, 2241 to 2280, 2281 to 2320, 2321 to 2360, 2361 to 2400, 2401 to 2440, 2441 to 2480, 2481 to 2520, 2521 to 2560, 2561 to 2600, 2601 to 2640, 2641 to 2680, 2681 to 2720, 2721 to 2760, 2761 to 2800, 2801 to 2840, 2841 to 2880, 2881 to 2920, 2921 to 2960, 2961 to 3000, 3001 to 3040, 3041 to 3080, 3081 to 3120, 3121 to 3160, 3161 to 3200, 3201 to 3240, 3241 to 3280, 3281 to 3320, 3321 to 3360, 3361 to 3400, 3401 to 3440, 3441 to 3480, 3481 to 3520, 3521 to 3560, 3561 to 3600, 3601 to 3640, 3641 to 3680, 3681 to 3720, 3721 to 3760, 3761 to 3800, 3801 to 3840, 3841 to 3880, 3881 to 3920, 3921 to 3960, 3961 to 4000, 4001 to 4040, 4041 to 4080, 4081 to 4120, 4121 to 4160, 4161 to 4200, 4201 to 4240, 4241 to 4280, 4281 to 4320, 4321 to 4360, 4361 to 4400, 4401 to 4440, 4441 to 4480, 4481 to 4520, 4521 to 4560, 4561 to 4600, 4601 to 4640, 4641 to 4680, 4681 to 4720, 4721 to 4760, 4761 to 4800, 4801 to 4840, 4841 to 4880, 4881 to 4920, 4921 to 4960, 4961 to 5000, 5001 to 5040, 5041 to 5080, 5081 to 5120, 5121 to 5160, 5161, 5200, 5201 to 5240, 5241 to 5280, 5281 to 5320, 5321 to 5360, 5361 to 5400, 5401 to 5440, 5441 to 5480, 5481 to 5520, and/or 5521 to 5552, of SEQ ID NO:1

In specific embodiments, the nucleic acid molecules hybridize to the complementary strand of nucleotides 1 to 688, 1 to 40, 41 to 80, 81 to 120, 121 to 160, 161 to 200, 201 to 240, 241 to 280, 281 to 320, 321 to 380, 381 to 420, 421 to 460,

461 to 500, 501 to 540, 541 to 580, 581 to 620, 621 to 660, 661 to 688, 301 to 612, 350 to 550 of SEQ ID NO:4.

In specific embodiments, the nucleic acid molecules hybridize to the complementary strand of nucleotides 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, 251 to 300, 301 to 350, 351 to 400, 401 to 450, 451 to 500, 501 to 550, 551 to 600, 600 to 650, 651 to 700, 701 to 750, 751 to 800, 800 to 850, 851 to 900, 901 to 950, and/or 951 to 985, of SEQ ID NO:7.

In specific embodiments, the nucleic acid molecules hybridize to the complementary strand of nucleotides 1 to 458, 806 to 1259, 352 to 663, 1 to 40, 41 to 80, 81 to 120, 121 to 160, 161 to 200, 201 to 240, 241 to 280, 281 to 320, 321 to 380, 381 to 420, 421 to 460, 760 to 805, 806 to 850, 851 to 890, 891 to 930, 931 to 970, 971 to 1010, 1011 to 1050, 1051 to 1090, 1091 to 1130, 1131 to 1170, 1171 to 1210, 1211 to 1250, 1221 to 1259, 311 to 351, 352 to 390, 391 to 430, 431 to 470, 471 to 510, 511 to 550, 551 to 590, 591 to 630, and/or 631 to 663 of SEQ ID NO:10.

As indicated, nucleic acid molecules of the present invention which encode full-length WF-HABP polypeptides may include, but are not limited to, those encoding the amino acid sequences of the full-length polypeptide (SEQ ID NO:2), by itself; the coding sequence for full-length polypeptide together with additional, non-coding sequences, including for example, but not limited to, introns and non-coding 5' and 3' sequences, such as the transcribed, non-translated sequences that play a role in transcription, mRNA processing, including splicing and polyadenylation signals, for example - ribosome binding and stability of mRNA; an additional coding sequence which codes for additional amino acids, such as those which provide additional functionalities. Thus, the sequence encoding the polypeptides may be fused to a marker sequence, such as a sequence encoding a peptide which facilitates purification of the fused polypeptide. In certain preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (Qiagen, Inc.), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. The "HA" tag is another peptide useful for purification which corresponds to an epitope derived from the influenza hemagglutinin protein, which has been described by Wilson et al., Cell 37:767 (1984). As discussed below, other such fusion proteins include full-length WF-HABPs fused to IgG-Fc at the N- or C-terminus.

As indicated, nucleic acid molecules of the present invention which encode WF-HABP polypeptides may include, but are not limited to, those encoding the amino acid sequences of the full-length polypeptide (SEQ ID NO:5), by itself; the coding sequence

for full-length polypeptide together with additional, non-coding sequences, including for example, but not limited to, introns and non-coding 5' and 3' sequences, such as the transcribed, non-translated sequences that play a role in transcription, mRNA processing, including splicing and polyadenylation signals, for example - ribosome binding and stability of mRNA; an additional coding sequence which codes for additional amino acids, such as those which provide additional functionalities. Thus, the sequence encoding the polypeptides may be fused to a marker sequence, such as a sequence encoding a peptide which facilitates purification of the fused polypeptide. In certain preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (Qiagen, Inc.), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. The "HA" tag is another peptide useful for purification which corresponds to an epitope derived from the influenza hemagglutinin protein, which has been described by Wilson et al., Cell 37:767 (1984). As discussed below, other such fusion proteins include WF-HABPs fused to IgG-Fc at the N- or C-terminus.

As indicated, nucleic acid molecules of the present invention which encode OE-HABP polypeptides may include, but are not limited to, those encoding the amino acid sequences of the full-length polypeptide (SEQ ID NO:8), by itself; the coding sequence for full-length polypeptide together with additional, non-coding sequences, including for example, but not limited to, introns and non-coding 5' and 3' sequences, such as the transcribed, non-translated sequences that play a role in transcription, mRNA processing, including splicing and polyadenylation signals, for example - ribosome binding and stability of mRNA; an additional coding sequence which codes for additional amino acids, such as those which provide additional functionalities. Thus, the sequence encoding the polypeptides may be fused to a marker sequence, such as a sequence encoding a peptide which facilitates purification of the fused polypeptide. In certain preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (Qiagen, Inc.), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. The "HA" tag is another peptide useful for purification which corresponds to an epitope derived from the influenza hemagglutinin protein, which has been described by Wilson et al., Cell 37:767 (1984). As discussed below, other such fusion proteins include OE-HABPs fused to IgG-Fc at the N- or C-terminus.

As indicated, nucleic acid molecules of the present invention which encode BM-HABP polypeptides may include, but are not limited to, those encoding the amino acid sequences of the full-length polypeptide (SEQ ID NO:11), by itself; the coding sequence for full-length polypeptide together with additional, non-coding sequences, including for example, but not limited to, introns and non-coding 5' and 3' sequences, such as the transcribed, non-translated sequences that play a role in transcription, mRNA processing, including splicing and polyadenylation signals, for example - ribosome binding and stability of mRNA; an additional coding sequence which codes for additional amino acids, such as those which provide additional functionalities. Thus, the sequence encoding the polypeptides may be fused to a marker sequence, such as a sequence encoding a peptide which facilitates purification of the fused polypeptide. In certain preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (Qiagen, Inc.), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. The "HA" tag is another peptide useful for purification which corresponds to an epitope derived from the influenza hemagglutinin protein, which has been described by Wilson et al., Cell 37:767 (1984). As discussed below, other such fusion proteins include BM-HABPs fused to IgG-Fc at the N- or C-terminus.

The present invention further relates to variants of the nucleic acid molecules of the present invention, which encode fragments (i.e., portions), analogs or derivatives of the full-length WF-HABP. Variants may occur naturally, such as a natural allelic variant. By an "allelic variant" is intended one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985). Non-naturally occurring variants may be produced using art-known mutagenesis techniques.

The present invention further relates to variants of the nucleic acid molecules of the present invention, which encode fragments (i.e., portions), analogs or derivatives of WF-HABP. Variants may occur naturally, such as a natural allelic variant. By an "allelic variant" is intended one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985). Non-naturally occurring variants may be produced using art-known mutagenesis techniques.

The present invention further relates to variants of the nucleic acid molecules of the present invention, which encode fragments (i.e., portions), analogs or derivatives of OE-HABP. Variants may occur naturally, such as a natural allelic variant. By an

"allelic variant" is intended one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985). Non-naturally occurring variants may be produced using art-known mutagenesis techniques.

5 The present invention further relates to variants of the nucleic acid molecules of the present invention, which encode fragments (i.e., portions), analogs or derivatives of BM-HABP. Variants may occur naturally, such as a natural allelic variant. By an "allelic variant" is intended one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985). Non-naturally occurring variants may be produced using art-known mutagenesis techniques.

10 Such variants include those produced by nucleotide substitutions, deletions or additions, which may involve one or more nucleotides. The variants may be altered in coding regions, non-coding regions, or both. Alterations in the coding regions may produce conservative or non-conservative amino acid substitutions, deletions or additions. Especially preferred among these are silent substitutions, additions and deletions, which do not alter the properties and activities of the full-length WF-HABP or fragments thereof. Also especially preferred in this regard are conservative substitutions.

15 Such variants include those produced by nucleotide substitutions, deletions or additions, which may involve one or more nucleotides. The variants may be altered in coding regions, non-coding regions, or both. Alterations in the coding regions may produce conservative or non-conservative amino acid substitutions, deletions or additions. Especially preferred among these are silent substitutions, additions and deletions, which do not alter the properties and activities of WF-HABP or fragments thereof. Also especially preferred in this regard are conservative substitutions.

20 Such variants include those produced by nucleotide substitutions, deletions or additions, which may involve one or more nucleotides. The variants may be altered in coding regions, non-coding regions, or both. Alterations in the coding regions may produce conservative or non-conservative amino acid substitutions, deletions or additions. Especially preferred among these are silent substitutions, additions and deletions, which do not alter the properties and activities of OE-HABP or fragments thereof. Also especially preferred in this regard are conservative substitutions.

25 Such variants include those produced by nucleotide substitutions, deletions or additions, which may involve one or more nucleotides. The variants may be altered in coding regions, non-coding regions, or both. Alterations in the coding regions may produce conservative or non-conservative amino acid substitutions, deletions or

additions. Especially preferred among these are silent substitutions, additions and deletions, which do not alter the properties and activities of BM-HABP or fragments thereof. Also especially preferred in this regard are conservative substitutions.

- Further embodiments of the invention include isolated nucleic acid molecules
- 5 comprising a polynucleotide having a nucleotide sequence at least 90% identical, and more preferably at least 95%, 96%, 97%, 98% or 99% identical to: (a) a nucleotide sequence encoding the full-length WF-HABP polypeptide having the complete (i.e., full-length) amino acid sequence shown in Figures 1A-H (SEQ ID NO:2); (b) a nucleotide encoding the complete amino sequence shown in Figures 1A-H but lacking
  - 10 the N-terminal methionine (amino acid residues 2 to 2100 in (SEQ ID NO:2)); (c) a nucleotide sequence encoding the full-length WF-HABP polypeptide having the amino acid sequence corresponding to the cDNA clone contained in ATCC Deposit Number 203503; (d) a nucleotide sequence encoding the full-length WF-HABP polypeptide having the amino acid sequence corresponding to the cDNA clone contained in ATCC
  - 15 Deposit Number 203503 but lacking the N-terminal methionine; (e) a nucleotide sequence encoding an HA binding motif (amino acid residues E-1791 to C-1894 of SEQ ID NO:2); (f) a nucleotide sequence encoding EGF-like Type 1 domains (amino acid residues from C-375 to C-386, amino acid residues from C-943 to C-954, amino acid residues from C-987 to C-998, , amino acid residues from C-1582 to C-1593, and
  - 20 amino acid residues from C-1626 to C-1637 of SEQ ID NO:2); (g) a nucleotide sequence encoding EGF-like Type 2 domains (amino acid residues from C-465 to C-478, amino acid residues from C-508 to C-521, amino acid residues from C-551 to C-564, amino acid residues from C-943 to C-957, amino acid residues from C-987 to C-998, amino acid residues from C-1027 to C-1040, amino acid residues from C-1069 to
  - 25 C-1082, amino acid residues from C-1111 to C-1125, amino acid residues from C-1582 to C-1596, amino acid residues from C-1582 to C-1596, amino acid residues from C-1626 to C-1637, amino acid residues from C-1663 to C-1676, amino acid residues from C-1747 to C-1760, and amino acid residues from C-1894 to C-1908 of SEQ ID NO:2); (h) a nucleotide sequence encoding a laminin-type EGF domain (amino
  - 30 acid residues from C-943 to C-977, and amino acid residues from C-1582 to C-1616 of SEQ ID NO:2 ); (I) a nucleotide sequence encoding a link protein domain (amino acid residues from C-1817 to C-1862 of SEQ ID NO:2); (j) a nucleotide sequence encoding a cytochrome P450 cysteine heme-iron ligand binding domains (amino acid residues from F-344 to G-353, and amino acid residues from W-514 to A-523 of SEQ ID
  - 35 NO:2); (k) a nucleotide sequence encoding a prokaryotic membrane lipoprotein lipid attachment site domains (amino acid residues from P-1103 to C-1113, and amino acid residues from T-1405 to C-1415 of SEQ ID NO:2); and (l) a nucleotide sequence

complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), (I), (j), (k), or (l).

Further embodiments of the invention include isolated nucleic acid molecules comprising a polynucleotide having a nucleotide sequence at least 90% identical, and more preferably at least 95%, 96%, 97%, 98% or 99% identical to: (a) a nucleotide sequence encoding the WF-HABP polypeptide having the complete (i.e., full-length) amino acid sequence shown in Figures 2A-B (SEQ ID NO:5); (b) a nucleotide encoding the complete amino sequence shown in Figures 2A-B but lacking the N-terminal methionine (amino acid residues 2 to 457 in (SEQ ID NO:5)); (c) a nucleotide sequence encoding the WF-HABP polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit Number 203503; (d) a nucleotide sequence encoding the WF-HABP polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit Number 203503 but lacking the N-terminal methionine; (e) a nucleotide sequence encoding the HA binding motif (amino acid residues E-91 to C-194 of SEQ ID NO:5); (f) a nucleotide sequence encoding the EGF-like Type 2 domain (amino acid residues C-194 to C-208, of SEQ ID NO:5); (g) the nucleotide sequence encoding the link domain (amino acid residues C-117 to C-162, of SEQ ID NO:5); (h) any fragment described herein; (i) the polypeptide sequence of Figures 2A-B (SEQ ID NO:5) minus a portion, or all of, the HA binding domain, the EGF-like Type 2 domain, and the link domain of WF-HABP shown in Figures 2A-B (SEQ ID NO:5); and (j) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), or (I).

Further embodiments of the invention include isolated nucleic acid molecules comprising a polynucleotide having a nucleotide sequence at least 90% identical, and more preferably at least 95%, 96%, 97%, 98% or 99% identical to: (a) a nucleotide sequence encoding the OE-HABP polypeptide having the complete (i.e., full-length) amino acid sequence shown in Figures 3A-B (SEQ ID NO:8); (b) a nucleotide encoding the complete amino sequence shown in Figures 3A-B but lacking the N-terminal methionine (amino acid residues 2 to 289 in (SEQ ID NO:8)); (c) a nucleotide sequence encoding the OE-HABP polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit Number 203501; (d) a nucleotide sequence encoding the OE-HABP polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit Number 203501 but lacking the N-terminal methionine; (e) a nucleotide sequence encoding the HA binding motif domain (amino acid residues P-97 to F-168, amino acid residues L-209 to C-286, of SEQ ID NO:8); (f) a nucleotide sequence encoding the link protein domain (amino acid residues C-188 to C-233 of SEQ ID NO:8); (g) any fragment described herein; (h) the polypeptide

sequence of Figures 3A-B (SEQ ID NO:8) minus a portion, or all of, the HA binding domain, and link protein domain of OE-HABP shown in Figures 3A-B (SEQ ID NO:8); and (i) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), or (h).

- 5 Further embodiments of the invention include isolated nucleic acid molecules comprising a polynucleotide having a nucleotide sequence at least 90% identical, and more preferably at least 95%, 96%, 97%, 98% or 99% identical to: (a) a nucleotide sequence encoding the BM-HABP polypeptide having the complete (i.e., full-length) amino acid sequence shown in Figures 4A-B (SEQ ID NO:11); (b) a nucleotide  
10 encoding the complete amino sequence shown in Figures 4A-B but lacking the N-terminal methionine (amino acid residues 2 to 353 in (SEQ ID NO:11)); (c) a nucleotide sequence encoding the BM-HABP polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit Number 203502; (d) a nucleotide sequence encoding the BM-HABP polypeptide having the amino acid sequence encoded  
15 by the cDNA clone contained in ATCC Deposit Number 203502 but lacking the N-terminal methionine; (e) a nucleotide sequence encoding the HA binding motif domain (amino acid residues Q-121 to L-215 in (SEQ ID NO:11)); (f) any fragment described herein; (g) the polypeptide sequence of Figures 4A-B (SEQ ID NO:11) minus a portion, or all of, the HA binding domain of BM-HABP shown in Figures 4A-B (SEQ ID  
20 NO:11); and (h) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), or (g).

- By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence encoding a full-length WF-HABP polypeptide is intended that the nucleotide sequence of the polynucleotide is identical to  
25 the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding a full-length WF-HABP. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another  
30 nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. These mutations of the reference sequence may occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among nucleotides in the reference sequence or in one or more contiguous groups  
35 within the reference sequence. The reference (query) sequence may be the entire full-length WF-HABP encoding nucleotide sequence shown in Figures 1A-H (SEQ ID NO:1) or any full-length WF-HABP polynucleotide fragment as described herein.



By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence encoding a WF-HABP polypeptide is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding WF-HABP. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. These mutations of the reference sequence may occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence. The reference (query) sequence may be the entire WF-HABP encoding nucleotide sequence shown in Figures 2A-B (SEQ ID NO:4) or any WF-HABP polynucleotide fragment as described herein.

By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence encoding a OE-HABP polypeptide is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding OE-HABP. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. These mutations of the reference sequence may occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence. The reference (query) sequence may be the entire OE-HABP encoding nucleotide sequence shown in Figures 3A-B (SEQ ID NO:7) or any OE-HABP polynucleotide fragment as described herein.

By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence encoding a BM-HABP polypeptide is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding BM-HABP. In

other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. These mutations of the reference sequence may occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence. The reference (query) sequence may be the entire BM-HABP encoding nucleotide sequence shown in Figures 4A-B (SEQ ID NO:10) or any BM-HABP polynucleotide fragment as described herein.

As a practical matter, whether any particular nucleic acid molecule is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the encoding nucleotide sequence shown in Figures 1A-H (SEQ ID NO:1), or to the nucleotide sequence of the deposited cDNA clone, can be determined conventionally using known computer programs such as the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711. Bestfit uses the local homology algorithm of Smith and Waterman, *Advances in Applied Mathematics* 2:482-489 (1981), to find the best segment of homology between two sequences. When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference nucleotide sequence and that gaps in homology of up to 5% of the total number of nucleotides in the reference sequence are allowed.

As a practical matter, whether any particular nucleic acid molecule is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the encoding nucleotide sequence shown in Figures 2A-B (SEQ ID NO:4), or to the nucleotide sequence of the deposited cDNA clone, can be determined conventionally using known computer programs such as the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711. Bestfit uses the local homology algorithm of Smith and Waterman, *Advances in Applied Mathematics* 2:482-489 (1981), to find the best segment of homology between two sequences. When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length

of the reference nucleotide sequence and that gaps in homology of up to 5% of the total number of nucleotides in the reference sequence are allowed.

As a practical matter, whether any particular nucleic acid molecule is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the encoding nucleotide sequence shown in Figures 3A-B (SEQ ID NO:7), or to the nucleotide sequence of the deposited cDNA clone, can be determined conventionally using known computer programs such as the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711. Bestfit uses the local homology algorithm of Smith and Waterman, *Advances in Applied Mathematics* 2:482-489 (1981), to find the best segment of homology between two sequences. When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference nucleotide sequence and that gaps in homology of up to 5% of the total number of nucleotides in the reference sequence are allowed.

As a practical matter, whether any particular nucleic acid molecule is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the encoding nucleotide sequence shown in Figures 4A-B (SEQ ID NO:10), or to the nucleotide sequence of the deposited cDNA clone, can be determined conventionally using known computer programs such as the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711. Bestfit uses the local homology algorithm of Smith and Waterman, *Advances in Applied Mathematics* 2:482-489 (1981), to find the best segment of homology between two sequences. When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference nucleotide sequence and that gaps in homology of up to 5% of the total number of nucleotides in the reference sequence are allowed.

In a specific embodiment, the identity between a reference (query) sequence (a sequence of the present full-length WF-HABP invention) and a subject sequence, also referred to as a global sequence alignment, is determined using the FASTDB computer program based on the algorithm of Brutlag et al. (*Comp. App. Biosci.* 6:237-245 (1990)). Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap

Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter. According to this embodiment, if the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction is made to the results to take into consideration the fact that the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. A determination of whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of this embodiment. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score. For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of this embodiment.

In a specific embodiment, the identity between a reference (query) sequence (a sequence of the present WF-HABP invention) and a subject sequence, also referred to as a global sequence alignment, is determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap

Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter. According to this embodiment, if the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction is made to the results to take into consideration the fact that the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. A determination of whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of this embodiment. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score. For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of this embodiment.

In a specific embodiment, the identity between a reference (query) sequence (a sequence of the present OE-HABP invention) and a subject sequence, also referred to as a global sequence alignment, is determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap

Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter. According to this embodiment, if the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction is made to the results to take into consideration the fact that the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. A determination of whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of this embodiment. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score. For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of this embodiment.

In a specific embodiment, the identity between a reference (query) sequence (a sequence of the present BM-HABP invention) and a subject sequence, also referred to as a global sequence alignment, is determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap

Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter. According to this embodiment, if the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction is made to the results to take into consideration the fact that the

5 FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. A

10 determination of whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of this embodiment. Only bases outside the 5' and 3' bases of the subject

15 sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score. For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of

20 the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared

25 with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual

30 corrections are made for the purposes of this embodiment.

The present application is directed to nucleic acid molecules at least 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequences (i.e., polynucleotides) disclosed herein, irrespective of whether they encode a polypeptide having full-length WF-HABP functional activity. This is because even where a particular nucleic acid

35 molecule does not encode a polypeptide having full-length WF-HABP functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer.

Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having full-length WF-HABP functional activity include, but are not limited to, *inter alia*, (1) isolating a full-length WF-HABP receptor gene or allelic or splice variants thereof in a cDNA library; (2) *in situ* hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of a full-length WF-HABP receptor gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); and (3) Northern Blot analysis for detecting full-length WF-HABP mRNA expression in specific tissues.

The present application is directed to nucleic acid molecules at least 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequences (i.e., polynucleotides) disclosed herein, irrespective of whether they encode a polypeptide having WF-HABP functional activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having WF-HABP functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having WF-HABP functional activity include, but are not limited to, *inter alia*, (1) isolating a WF-HABP receptor gene or allelic or splice variants thereof in a cDNA library; (2) *in situ* hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of a WF-HABP receptor gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); and (3) Northern Blot analysis for detecting WF-HABP mRNA expression in specific tissues.

The present application is directed to nucleic acid molecules at least 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequences (i.e., polynucleotides) disclosed herein, irrespective of whether they encode a polypeptide having OE-HABP functional activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having OE-HABP functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having OE-HABP functional activity include, but are not limited to, *inter alia*, (1) isolating a OE-HABP receptor gene or allelic or splice variants thereof in a cDNA library; (2) *in situ* hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of a OE-HABP receptor gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); and (3) Northern Blot analysis for detecting OE-HABP mRNA expression in specific tissues.



The present application is directed to nucleic acid molecules at least 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequences (i.e., polynucleotides) disclosed herein, irrespective of whether they encode a polypeptide having BM-HABP functional activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having BM-HABP functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having BM-HABP functional activity include, but are not limited to, *inter alia*, (1) isolating a BM-HABP receptor gene or allelic or splice variants thereof in a cDNA library; (2) *in situ* hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of a BM-HABP receptor gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); and (3) Northern Blot analysis for detecting BM-HABP mRNA expression in specific tissues.

Preferred, however, are nucleic acid molecules having sequences at least 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequences disclosed herein, which do, in fact, encode a polypeptide having full-length WF-HABP functional activity. By "a polypeptide having full-length WF-HABP receptor functional activity" is intended polypeptides exhibiting activity similar, but not necessarily identical, to an activity of full-length WF-HABPs of the present invention (either the full-length polypeptide, or the splice variants), as measured, for example, in a particular immunoassay or biological assay. For example, full-length WF-HABP activity can be measured by determining the ability of a full-length WF-HABP polypeptide to bind a full-length WF-HABP ligand (e.g., hyaluronan, or chondroitin sulfate proteoglycan). The full-length WF-HABP receptor activity may also be measured by determining the ability of a polypeptide, such as cognate ligand which is free or expressed on a cell surface, to induce cellular proliferation, cellular adhesion, or cellular migration.

Preferred, however, are nucleic acid molecules having sequences at least 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequences disclosed herein, which do, in fact, encode a polypeptide having WF-HABP functional activity. By "a polypeptide having WF-HABP receptor functional activity" is intended polypeptides exhibiting activity similar, but not necessarily identical, to an activity of WF-HABPs of the present invention (either the full-length polypeptide, or the splice variants), as measured, for example, in a particular immunoassay or biological assay. For example, WF-HABP activity can be measured by determining the ability of a WF-HABP polypeptide to bind a WF-HABP ligand (e.g., hyaluronan, or chondroitin sulfate

proteoglycan). WF-HABP receptor activity may also be measured by determining the ability of a polypeptide, such as cognate ligand which is free or expressed on a cell surface, to induce cellular proliferation, cellular adhesion, or cellular migration.

Preferred, however, are nucleic acid molecules having sequences at least 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequences disclosed herein, which do, in fact, encode a polypeptide having OE-HABP functional activity. By "a polypeptide having OE-HABP receptor functional activity" is intended polypeptides exhibiting activity similar, but not necessarily identical, to an activity of OE-HABPs of the present invention (either the full-length polypeptide, or the splice variants), as measured, for example, in a particular immunoassay or biological assay. For example, OE-HABP activity can be measured by determining the ability of a OE-HABP polypeptide to bind a OE-HABP ligand (e.g., hyaluronan, or chondroitin sulfate proteoglycan). OE-HABP receptor activity may also be measured by determining the ability of a polypeptide, such as cognate ligand which is free or expressed on a cell surface, to induce cellular proliferation, cellular adhesion, or cellular migration.

Preferred, however, are nucleic acid molecules having sequences at least 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequences disclosed herein, which do, in fact, encode a polypeptide having BM-HABP functional activity. By "a polypeptide having BM-HABP receptor functional activity" is intended polypeptides exhibiting activity similar, but not necessarily identical, to an activity of BM-HABPs of the present invention (either the full-length polypeptide, or the splice variants), as measured, for example, in a particular immunoassay or biological assay. For example, BM-HABP activity can be measured by determining the ability of a BM-HABP polypeptide to bind a BM-HABP ligand (e.g., hyaluronan, or chondroitin sulfate proteoglycan). BM-HABP receptor activity may also be measured by determining the ability of a polypeptide, such as cognate ligand which is free or expressed on a cell surface, to induce cellular proliferation, cellular adhesion, or cellular migration.

Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 90%, 95%, 96%, 97%, 98%, or 99% identical to the nucleic acid sequence shown in Figures 1A-H (SEQ ID NO:1), or fragments thereof, will encode polypeptides "having full-length WF-HABP functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having full-length WF-HABP functional

activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid).

Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 90%, 95%, 96%, 97%, 98%, or 99% identical to the nucleic acid sequence of the deposited cDNA, the nucleic acid sequence shown in Figures 2A-B (SEQ ID NO:4), or fragments thereof, will encode polypeptides "having WF-HABP functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having WF-HABP functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid).

Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 90%, 95%, 96%, 97%, 98%, or 99% identical to the nucleic acid sequence of the deposited cDNA, the nucleic acid sequence shown in Figures 3A-B (SEQ ID NO:7), or fragments thereof, will encode polypeptides "having OE-HABP functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having OE-HABP functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid).

Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 90%, 95%, 96%, 97%, 98%, or 99% identical to the nucleic acid sequence of the deposited cDNA, the nucleic acid sequence shown in Figures 4A-B (SEQ ID NO:10), or fragments thereof, will encode polypeptides "having BM-HABP functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will

be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having BM-HABP functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid).

For example, guidance concerning how to make phenotypically silent amino acid substitutions of the full-length WF-HABP invention is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990), wherein the authors indicate that proteins are surprisingly tolerant of amino acid substitutions.

For example, guidance concerning how to make phenotypically silent amino acid substitutions of the WF-HABP invention is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990), wherein the authors indicate that proteins are surprisingly tolerant of amino acid substitutions.

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For example, guidance concerning how to make phenotypically silent amino acid substitutions of the BM-HABP invention is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990), wherein the authors indicate that proteins are surprisingly tolerant of amino acid substitutions.

### Vectors and Host Cells

The present invention also relates to vectors which include the isolated DNA molecules (i.e., polynucleotides) of the present invention, host cells which are genetically engineered with the recombinant vectors, and the production of full-length WF-HABP polypeptides or fragments thereof using these host cells or host cells that have otherwise been genetically engineered using techniques known in the art to express a polypeptide of the invention.

The present invention also relates to vectors which include the isolated DNA molecules (i.e., polynucleotides) of the present invention, host cells which are genetically engineered with the recombinant vectors, and the production of WF-HABP polypeptides or fragments thereof using these host cells or host cells that have

otherwise been genetically engineered using techniques known in the art to express a polypeptide of the invention.

5 The present invention also relates to vectors which include the isolated DNA molecules (i.e., polynucleotides) of the present invention, host cells which are genetically engineered with the recombinant vectors, and the production of OE-HABP polypeptides or fragments thereof using these host cells or host cells that have otherwise been genetically engineered using techniques known in the art to express a polypeptide of the invention.

10 The present invention also relates to vectors which include the isolated DNA molecules (i.e., polynucleotides) of the present invention, host cells which are genetically engineered with the recombinant vectors, and the production of BM-HABP polypeptides or fragments thereof using these host cells or host cells that have otherwise been genetically engineered using techniques known in the art to express a polypeptide of the invention.

15 The full-length WF-HABP polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged *in vitro* using an appropriate packaging cell line and then transduced into host cells.

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30 The BM-HABP polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged *in vitro* using an appropriate packaging cell line and then transduced into host cells.

35 In one embodiment, a polynucleotide of the full-length WF-HABP invention are operatively associated with an appropriate heterologous regulatory element (e.g., promoter or enhancer), such as the phage lambda PL promoter, the *E. coli* lac, trp and

tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters or enhancers will be known to the skilled artisan.

In one embodiment, a polynucleotide of the WF-HABP invention are operatively associated with an appropriate heterologous regulatory element (e.g., promoter or enhancer), such as the phage lambda PL promoter, the *E. coli* lac, trp and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters or enhancers will be known to the skilled artisan.

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In full-length WF-HABP embodiments in which vectors contain expression constructs, these constructs will further contain sites for transcription initiation, termination and, in the transcribed region, a ribosome binding site for translation. The coding portion of the mature transcripts expressed by the vector expression constructs will preferably include a translation initiating at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

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As indicated, the full-length WF-HABP expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase or neomycin resistance for eukaryotic cell culture and tetracycline or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate heterologous hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from Qiagen; pHE4, pA2; and PO4, pBS vectors, Phagescript vectors, Bluescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene; and ptrc99a, pKK223-3, pKK233-3, pWF-HABP40, pRIT5 available from Pharmacia. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

Selection of appropriate vectors and promoters for expression in a host cell is a well known procedure and the requisite techniques for expression vector construction, introduction of the vector into the host and expression in the host are routine skills in the art.

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Selection of appropriate vectors and promoters for expression in a host cell is a well known procedure and the requisite techniques for expression vector construction, introduction of the vector into the host and expression in the host are routine skills in the art.

As indicated, the OE-HABP expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase or neomycin resistance for eukaryotic cell culture and tetracycline or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate heterologous hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

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Selection of appropriate vectors and promoters for expression in a host cell is a well known procedure and the requisite techniques for expression vector construction, introduction of the vector into the host and expression in the host are routine skills in the art.

As indicated, the BM-HABP expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase or neomycin resistance for eukaryotic cell culture and tetracycline or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate heterologous hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS



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Selection of appropriate vectors and promoters for expression in a host cell is a well known procedure and the requisite techniques for expression vector construction, introduction of the vector into the host and expression in the host are routine skills in the art.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., full-length WF-HABP coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with full-length WF-HABP polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous full-length WF-HABP polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous full-length WF-HABP polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., WF-HABP coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with WF-HABP polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous WF-HABP polynucleotides. For example, techniques known in the art may be used to operably

associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous WF-HABP polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

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The host cell can be a higher eukaryotic cell, such as a mammalian cell (e.g., a human derived cell), or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. The host strain may be chosen which modulates the expression of the inserted full-length WF-HABP gene sequences, or  
 5 modifies and processes the gene product in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain inducers; thus expression of the genetically engineered polypeptide may be controlled. Furthermore, different host cells have characteristics and specific mechanisms for the translational and post-translational processing and modification (e.g., glycosylation, phosphorylation,  
 10 cleavage) of proteins. Appropriate cell lines can be chosen to ensure the desired modifications and processing of the foreign protein expressed.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection or other methods. Such methods  
 15 are described in many standard laboratory manuals, such as Davis et al., *Basic Methods In Molecular Biology* (1986).

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The full-length WF-HABP polypeptide may be expressed in a modified form, such as a fusion protein (comprising the polypeptide joined via a peptide bond to a heterologous protein sequence (of a different protein)), and may include not only secretion signals, but also additional heterologous functional regions. Such a fusion protein can be made by ligating polynucleotides of the invention and the desired nucleic acid sequence encoding the desired amino acid sequence to each other, by methods known in the art, in the proper reading frame, and expressing the fusion protein product by methods known in the art. Alternatively, such a fusion protein can be made by protein synthetic techniques, e.g., by use of a peptide synthesizer. Thus, for instance, a region of additional amino acids, particularly charged amino acids, may be added to

the N-terminus of the polypeptide to improve stability and persistence in the host cell, during purification, or during subsequent handling and storage. Additionally, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to polypeptides to engender secretion or excretion, to improve stability and to facilitate purification, among others, are familiar and routine techniques in the art. A preferred fusion protein comprises a heterologous region from immunoglobulin that is useful to solubilize proteins. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is thoroughly advantageous for use in therapy and diagnosis and thus results, for example, in improved pharmacokinetic properties (EP-A 0232 262). On the other hand, for some uses it would be desirable to be able to delete the Fc part after the fusion protein has been expressed, detected and purified in the advantageous manner described. This is the case when Fc portion proves to be a hindrance to use in therapy and diagnosis, for example when the fusion protein is to be used as antigen for immunizations. In drug discovery, for example, human proteins, such as, human hIL-5 receptor have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. See, Bennett et al., J. Mol. Recog. 8:52-58 (1995) and Johanson et al., J. Biol. Chem. 270(16):9459-9471 (1995).

The WF-HABP polypeptide may be expressed in a modified form, such as a fusion protein (comprising the polypeptide joined via a peptide bond to a heterologous protein sequence (of a different protein)), and may include not only secretion signals, but also additional heterologous functional regions. Such a fusion protein can be made by ligating polynucleotides of the invention and the desired nucleic acid sequence encoding the desired amino acid sequence to each other, by methods known in the art, in the proper reading frame, and expressing the fusion protein product by methods known in the art. Alternatively, such a fusion protein can be made by protein synthetic techniques, e.g., by use of a peptide synthesizer. Thus, for instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence in the host cell, during purification, or during subsequent handling and storage. Additionally, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to polypeptides to engender secretion or excretion, to improve stability and to facilitate purification, among others, are familiar and routine techniques in the art. A preferred

fusion protein comprises a heterologous region from immunoglobulin that is useful to solubilize proteins. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is thoroughly advantageous for use in therapy and diagnosis and thus results, for example, in improved pharmacokinetic properties (EP-A 0232 262). On the other hand, for some uses it would be desirable to be able to delete the Fc part after the fusion protein has been expressed, detected and purified in the advantageous manner described. This is the case when Fc portion proves to be a hindrance to use in therapy and diagnosis, for example when the fusion protein is to be used as antigen for immunizations. In drug discovery, for example, human proteins, such as, human hIL-5 receptor have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. See, Bennett et al., J. Mol. Recog. 8:52-58 (1995) and Johanson et al., J. Biol. Chem. 270(16):9459-9471 (1995).

The OE-HABP polypeptide may be expressed in a modified form, such as a fusion protein (comprising the polypeptide joined via a peptide bond to a heterologous protein sequence (of a different protein)), and may include not only secretion signals, but also additional heterologous functional regions. Such a fusion protein can be made by ligating polynucleotides of the invention and the desired nucleic acid sequence encoding the desired amino acid sequence to each other, by methods known in the art, in the proper reading frame, and expressing the fusion protein product by methods known in the art. Alternatively, such a fusion protein can be made by protein synthetic techniques, e.g., by use of a peptide synthesizer. Thus, for instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence in the host cell, during purification, or during subsequent handling and storage. Additionally, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to polypeptides to engender secretion or excretion, to improve stability and to facilitate purification, among others, are familiar and routine techniques in the art. A preferred fusion protein comprises a heterologous region from immunoglobulin that is useful to solubilize proteins. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is thoroughly advantageous for use in therapy and diagnosis and thus results, for example, in improved pharmacokinetic properties (EP-A

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The BM-HABP polypeptide may be expressed in a modified form, such as a fusion protein (comprising the polypeptide joined via a peptide bond to a heterologous protein sequence (of a different protein)), and may include not only secretion signals, but also additional heterologous functional regions. Such a fusion protein can be made by ligating polynucleotides of the invention and the desired nucleic acid sequence encoding the desired amino acid sequence to each other, by methods known in the art, in the proper reading frame, and expressing the fusion protein product by methods known in the art. Alternatively, such a fusion protein can be made by protein synthetic techniques, e.g., by use of a peptide synthesizer. Thus, for instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence in the host cell, during purification, or during subsequent handling and storage. Additionally, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to polypeptides to engender secretion or excretion, to improve stability and to facilitate purification, among others, are familiar and routine techniques in the art. A preferred fusion protein comprises a heterologous region from immunoglobulin that is useful to solubilize proteins. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is thoroughly advantageous for use in therapy and diagnosis and thus results, for example, in improved pharmacokinetic properties (EP-A 0232 262). On the other hand, for some uses it would be desirable to be able to delete the Fc part after the fusion protein has been expressed, detected and purified in the advantageous manner described. This is the case when Fc portion proves to be a hindrance to use in therapy and diagnosis, for example when the fusion protein is to be used as antigen for immunizations. In drug discovery, for example, human proteins, such as, human hIL-5 receptor have been fused with Fc portions for the purpose of

high-throughput screening assays to identify antagonists of hIL-5. See, Bennett et al., J. Mol. Recog. 8:52-58 (1995) and Johanson et al., J. Biol. Chem. 270(16):9459-9471 (1995).

5 Full-length WF-HABP polypeptides (including fragments, variants, derivatives, and analogs thereof) can be recovered and purified from recombinant cell cultures by standard methods which include, but are not limited to, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most  
10 preferably, high performance liquid chromatography ("HPLC") is employed for purification. Polypeptides of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect and mammalian cells. Depending upon the host employed in  
15 a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, or alternatively, may be missing the N-terminal methionine, in some cases as a result of host-mediated processes.

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35 processes.

OE-HABP polypeptides (including fragments, variants, derivatives, and analogs thereof) can be recovered and purified from recombinant cell cultures by



standard methods which include, but are not limited to, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification. Polypeptides of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, or alternatively, may be missing the N-terminal methionine, in some cases as a result of host-mediated processes.

BM-HABP polypeptides (including fragments, variants, derivatives, and analogs thereof) can be recovered and purified from recombinant cell cultures by standard methods which include, but are not limited to, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification. Polypeptides of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, or alternatively, may be missing the N-terminal methionine, in some cases as a result of host-mediated processes.

#### **WF-HABP Polypeptides and Fragments**

The invention further provides isolated full-length WF-HABP polypeptides corresponding to the amino acid sequence depicted in Figures 1A-H (SEQ ID NO:2), or a polypeptide comprising a fragment (i.e., portion) of the above polypeptides.

The polypeptides of the full-length WF-HABP invention may be membrane bound or may be in a soluble circulating form. Soluble peptides are defined by amino

acid sequence wherein the sequence comprises the polypeptide sequence lacking transmembrane domains.

The invention further provides isolated WF-HABP polypeptides having the amino acid sequence encoded by the deposited cDNA (i.e., clone HWFBG79), the amino acid sequence depicted in Figures 2A-B (SEQ ID NO:5), or a polypeptide comprising a fragment (i.e., portion) of the above polypeptides.

The polypeptides of the WF-HABP invention may be membrane bound or may be in a soluble circulating form. Soluble peptides are defined by amino acid sequence wherein the sequence comprises the polypeptide sequence lacking transmembrane domains.

The invention further provides isolated OE-HABP polypeptides having the amino acid sequence encoded by the deposited cDNA (i.e., clone HOEDH76), the amino acid sequence depicted in Figures 3A-B (SEQ ID NO:8), or a polypeptide comprising a fragment (i.e., portion) of the above polypeptides.

The polypeptides of the OE-HABP invention may be membrane bound or may be in a soluble circulating form. Soluble peptides are defined by amino acid sequence wherein the sequence comprises the polypeptide sequence lacking transmembrane domains.

The invention further provides isolated BM-HABP polypeptides having the amino acid sequence encoded by the deposited cDNA (i.e., clone HB MVC21), the amino acid sequence depicted in Figures 4A-B (SEQ ID NO:11), or a polypeptide comprising a fragment (i.e., portion) of the above polypeptides.

The polypeptides of the BM-HABP invention may be membrane bound or may be in a soluble circulating form. Soluble peptides are defined by amino acid sequence wherein the sequence comprises the polypeptide sequence lacking transmembrane domains.

The polypeptides of the present invention are preferably provided in an isolated form. By "isolated polypeptide", is intended a polypeptide removed from its native environment. Thus, a polypeptide produced and contained within a recombinant host cell would be considered "isolated" for purposes of the present invention. Also intended as an "isolated polypeptide" are polypeptides that have been purified, partially or substantially, from a recombinant host. For example, recombinantly produced versions of the full-length WF-HABP polypeptides can be substantially purified by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988).

The polypeptides of the present invention are preferably provided in an isolated form. By "isolated polypeptide", is intended a polypeptide removed from its native environment. Thus, a polypeptide produced and contained within a recombinant host

cell would be considered "isolated" for purposes of the present invention. Also intended as an "isolated polypeptide" are polypeptides that have been purified, partially or substantially, from a recombinant host. For example, recombinantly produced versions of WF-HABP polypeptides can be substantially purified by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988).

The polypeptides of the present invention are preferably provided in an isolated form. By "isolated polypeptide", is intended a polypeptide removed from its native environment. Thus, a polypeptide produced and contained within a recombinant host cell would be considered "isolated" for purposes of the present invention. Also intended as an "isolated polypeptide" are polypeptides that have been purified, partially or substantially, from a recombinant host. For example, recombinantly produced versions of OE-HABP polypeptides can be substantially purified by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988).

The polypeptides of the present invention are preferably provided in an isolated form. By "isolated polypeptide", is intended a polypeptide removed from its native environment. Thus, a polypeptide produced and contained within a recombinant host cell would be considered "isolated" for purposes of the present invention. Also intended as an "isolated polypeptide" are polypeptides that have been purified, partially or substantially, from a recombinant host. For example, recombinantly produced versions of BM-HABP polypeptides can be substantially purified by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988).

Polypeptide fragments of the present invention include polypeptides comprising or alternatively, consisting of, an amino acid sequence contained in SEQ ID NO:2, or corresponding to nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide shown in Figures 1A-H (SEQ ID NO:1) or the complementary strand thereto. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments that comprise or alternatively, consist of from amino acid residues: 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, 251 to 300, 301 to 350, 321 to 333, 351 to 400, 401 to 450, 451 to 500, 501 to 550, 551 to 600, 576 to 606, 601 to 650, 651 to 700, 701 to 750, 751 to 800, 801 to 850, 851 to 900, 901 to 950, 1001 to 1050, 1051 to 1100, 1101 to 1150, 1151 to 1200, 1201 to 1250, 1251 to 1300, 1301 to 1350, 1351 to 1400, 1401 to 1450, 1451 to 1500, 1501 to 1550, 1551 to 1600, 1601 to 1650, 1651 to 1700, 1701 to 1750, 1751 to 1800, 1801 to 1850, 1851 to 1900, 1901 to 1950, 1951 to 2000, 2001 to 2050, 2051 to 2100 of SEQ ID NO:2. Moreover, polypeptide fragments can

be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1000, 1250, 1500, 1750, 2000, or 2100 amino acids in length.

Polypeptide fragments of the present invention include polypeptides comprising  
 5 or alternatively, consisting of, an amino acid sequence contained in SEQ ID NO:5, corresponding to the cDNA contained in the deposited clone, or corresponding to nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone, or shown in Figures 2A-B (SEQ ID NO:5) or the complementary strand thereto. Protein fragments may be "free-  
 10 standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments that comprise or alternatively, consist of from amino acid residues: 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, 251 to 300, 301 to 350, 321 to 333, 351 to 400, 401 to 450, and/or 451 to 457 of SEQ ID NO:2. Moreover, polypeptide fragments can be at least  
 15 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175, 200, 250, 300, 350, 400, 450, or 457 amino acids in length.

Polypeptide fragments of the present invention include polypeptides comprising  
 or alternatively, consisting of, an amino acid sequence contained in SEQ ID NO:8,  
 20 corresponding to the cDNA contained in the deposited clone, or corresponding to nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone, or shown in Figures 3A-B (SEQ ID NO:8) or the complementary strand thereto. Protein fragments may be "free-  
 25 standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments that comprise or alternatively, consist of from amino acid residues: 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, and/or 251 to 289 of SEQ ID NO:5. Moreover, polypeptide  
 30 fragments can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175, 200, 250, or 289 amino acids in length.

Polypeptide fragments of the present invention include polypeptides comprising  
 or alternatively, consisting of, an amino acid sequence contained in SEQ ID NO:11,  
 corresponding to the cDNA contained in the deposited clone, or corresponding to  
 35 nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone, or shown in Figures 4A-B (SEQ ID NO:11) or the complementary strand thereto. Protein fragments may be "free-  
 standing," or comprised within a larger polypeptide of which the fragment forms a part

or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments that comprise or alternatively, consist of from amino acid residues: 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, 251 to 300, 301 to 350, 351 to 353, of SEQ ID NO:11.

5 Moreover, polypeptide fragments can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175, 200, 250, 300, 350, or 353 amino acids in length.

In additional embodiments, the polypeptide fragments of the invention comprise, or alternatively consist, of one or more full-length WF-HABP receptor domains. In particular embodiments, such polypeptide fragments comprise, or alternatively, consist of: (a) an HA binding motif (amino acid residues E-1791 to C-1894 of SEQ ID NO:2); (b) EGF-like Type 1 domains (amino acid residues from C-375 to C-386, amino acid residues from C-943 to C-954, amino acid residues from C-987 to C-998, amino acid residues from C-1582 to C-1593, and amino acid residues from C-1626 to C-1637 of SEQ ID NO:2); (c) EGF-like Type 2 domains (amino acid residues from C-465 to C-478, amino acid residues from C-508 to C-521, amino acid residues from C-551 to C-564, amino acid residues from C-943 to C-957, amino acid residues from C-987 to C-998, amino acid residues from C-1027 to C-1040, amino acid residues from C-1069 to C-1082, amino acid residues from C-1111 to C-1125, amino acid residues from C-1582 to C-1596, amino acid residues from C-1582 to C-1596, amino acid residues from C-1626 to C-1637, amino acid residues from C-1663 to C-1676, amino acid residues from C-1747 to C-1760, and amino acid residues from C-1894 to C-1908 of SEQ ID NO:2); (d) a laminin-type EGF domain (amino acid residues from C-943 to C-977, and amino acid residues from C-1582 to C-1616 of SEQ ID NO:2); (e) a link protein domain (amino acid residues from C-1817 to C-1862 of SEQ ID NO:2); (f) a cytochrome P450 cysteine heme-iron ligand binding domains (amino acid residues from F-344 to G-353, and amino acid residues from W-514 to A-523 of SEQ ID NO:2); (g) a prokaryotic membrane lipoprotein lipid attachment site domains (amino acid residues from P-1103 to C-1113, and amino acid residues from T-1405 to C-1415 of SEQ ID NO:2 or (h) any combination of polypeptides (a) -(g).

30 In additional embodiments, the polypeptide fragments of the invention comprise, or alternatively consist, of one or more WF-HABP receptor domains. In particular embodiments, such polypeptide fragments comprise, or alternatively, consist of: (a) an HA binding motif (amino acid residues E-91 to C-194 of SEQ ID NO:5); (b) an EGF-like Type 2 domain (amino acid residues C-194 to C-208, of SEQ ID NO:5); (c) a link domain (amino acid residues C-117 to C-162, of SEQ ID NO:5); (d) any fragment described herein; (e) the polypeptide sequence of Figures 2A-B (SEQ ID NO:5) minus a portion, or all of, the HA binding domain, the EGF-like Type 2 domain,

35

and the link domain of WF-HABP shown in Figures 2A-B (SEQ ID NO:5); and (f) any combination of polypeptides (a) -(e).

In additional embodiments, the polypeptide fragments of the invention comprise, or alternatively consist, of one or more OE-HABP receptor domains. In particular embodiments, such polypeptide fragments comprise, or alternatively, consist of: (a) an HA binding motif domain (amino acid residues P-97 to F-168, amino acid residues L-209 to C-286, of SEQ ID NO:8); (b) a link protein domain (amino acid residues C-188 to C-233 of SEQ ID NO:8); (c) any fragment described herein, (d) the polypeptide sequence of Figures 3A-B (SEQ ID NO:8) minus a portion, or all of, the HA binding domain, and the link domain of OE-HABP shown in Figures 3A-B (SEQ ID NO:8); and (e) any combination of polypeptides (a) -(d).

In additional embodiments, the polypeptide fragments of the invention comprise, or alternatively consist, of one or more BM-HABP receptor domains. In particular embodiments, such polypeptide fragments comprise, or alternatively, consist of: (a) an HA binding motif domain (amino acid residues Q-121 to L-215 in (SEQ ID NO:11)); (b) any fragment described herein; (c) the polypeptide sequence of Figures 4A-B (SEQ ID NO:11) minus a portion, or all of, the HA binding domain of BM-HABP shown in Figures 4A-B (SEQ ID NO:11); and (d) any combination of polypeptides (a) -(c).

Among the especially preferred fragments of the invention are fragments characterized by structural or functional attributes of the full-length WF-HABP. Such fragments include amino acid residues that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet-forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, surface forming regions, and high antigenic index regions (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) of full-length WF-HABP (SEQ ID NO:2). Certain preferred regions are those set out in Figure 3 and include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence depicted in Figures 1A-H (SEQ ID NO:2), such preferred regions include; Garnier-Robson predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Kyte-Doolittle predicted hydrophilic and hydrophobic regions; Eisenberg alpha and beta amphipathic regions; Emini surface-forming regions; and Jameson-Wolf high antigenic index

regions, as predicted using the default parameters of these computer programs. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Among the especially preferred fragments of the invention are fragments characterized by structural or functional attributes of WF-HABP. Such fragments

5 include amino acid residues that comprise alpha-helix and alpha-helix forming regions (“alpha-regions”), beta-sheet and beta-sheet-forming regions (“beta-regions”), turn and turn-forming regions (“turn-regions”), coil and coil-forming regions (“coil-regions”), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, surface forming regions, and high antigenic index regions (i.e., containing

10 four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) of WF-HABP (SEQ ID NO:5). Certain preferred regions are those set out in Figure 3 and include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence depicted in Figures 2A-B (SEQ ID NO:5), such

15 preferred regions include; Garnier-Robson predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Kyte-Doolittle predicted hydrophilic and hydrophobic regions; Eisenberg alpha and beta amphipathic regions; Emini surface-forming regions; and Jameson-Wolf high antigenic index regions, as predicted using the default

20 parameters of these computer programs. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Among the especially preferred fragments of the invention are fragments characterized by structural or functional attributes of the OE-HABP. Such fragments

25 include amino acid residues that comprise alpha-helix and alpha-helix forming regions (“alpha-regions”), beta-sheet and beta-sheet-forming regions (“beta-regions”), turn and turn-forming regions (“turn-regions”), coil and coil-forming regions (“coil-regions”), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, surface forming regions, and high antigenic index regions (i.e., containing

30 four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) of OE-HABP (SEQ ID NO:8). Certain preferred regions are those set out in Figure 3 and include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence depicted in Figures 3A-B (SEQ ID NO:8), such

35 preferred regions include; Garnier-Robson predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Kyte-Doolittle predicted hydrophilic and hydrophobic regions; Eisenberg alpha and beta amphipathic regions; Emini surface-forming regions;

and Jameson-Wolf high antigenic index regions, as predicted using the default parameters of these computer programs. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Among the especially preferred fragments of the invention are fragments  
 5 characterized by structural or functional attributes of the BM-HABP. Such fragments include amino acid residues that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet-forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic  
 10 regions, surface forming regions, and high antigenic index regions (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) of BM-HABP (SEQ ID NO:11). Certain preferred regions are those set out in Figure 3 and include, but are not limited to, regions of the aforementioned types identified by  
 15 analysis of the amino acid sequence depicted in Figures 4A-B (SEQ ID NO:11), such preferred regions include; Garnier-Robson predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Kyte-Doolittle predicted hydrophilic and hydrophobic regions; Eisenberg alpha and beta amphipathic regions; Emini surface-forming regions;  
 20 and Jameson-Wolf high antigenic index regions, as predicted using the default parameters of these computer programs. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In specific embodiments, polypeptide fragments of the full-length WF-HABP invention comprise, or alternatively consist of, amino acid residues: 365 to 375, 376 to  
 25 385, 386 to 395, 396 to 405, 406 to 415, 416 to 425, 426 to 435, 436 to 445, 446 to 455, 456 to 465, 466 to 475, 476 to 485, 486 to 495, 496 to 505, 506 to 515, 516 to 525, 526 to 535, 536 to 545, 546 to 555, 556 to 565, 566 to 575, 576 to 585, 586 to 595, 596 to 605, 606 to 615, 616 to 625, 626 to 635, 636 to 645, 646 to 655, 656 to 665, 666 to 675, 676 to 685, 686 to 695, 696 to 705, 706 to 715, 716 to 725, 726 to  
 30 735, 736 to 745, 746 to 755, 756 to 765, 766 to 775, 776 to 785, 786 to 795, 796 to 805, 806 to 815, 816 to 825, 826 to 835, 836 to 845, 846 to 855, 856 to 865, 866 to 875, 876 to 885, 886 to 895, 896 to 905, 906 to 915, 916 to 925, 926 to 935, 936 to 945, 946 to 955, 956 to 965, 966 to 975, 976 to 985, 986 to 995, 996 to 1005, 1006 to 1015, 1016 to 1025, 1026 to 1035, 1036 to 1045, 1046 to 1055, 1056 to 1065, 1066  
 35 to 1075, 1076 to 1085, 1086 to 1095, 1096 to 1105, 1106 to 1115, 1116 to 1125, 1126 to 1135, 1136 to 1145, 1146 to 1155, 1156 to 1165, 1166 to 1175, 1176 to 1185, 1186 to 1195, 1196 to 1205, 1206, 1215, 1216 to 1225, 1226 to 1235, 1236 to



1245, 1246 to 1255, 1256 to 1265, 1266 to 1275, 1276 to 1285, 1286 to 1295, 1296 to 1305, 1306 to 1315, 1316 to 1325, 1326 to 1335, 1336 to 1345, 1346 to 1355, 1356 to 1365, 1366 to 1375, 1376 to 1385, 1386 to 1395, 1396 to 1405, 1406 to 1415, 1416 to 1425, 1426 to 1435, 1436 to 1445, 1446 to 1455, 1456 to 1465, 1466 to 1475, 1476 to 1485, 1486 to 1495, 1496 to 1505, 1506 to 1515, 1516 to 1525, 1526 to 1535, 1536 to 1545, 1546 to 1555, 1556 to 1565, 1566 to 1575, 1576 to 1585, 1586 to 1595, 1605, 1606 to 1615, 1616 to 1625, 1626 to 1635, 1636 to 1645, 1646 to 1655, 1656 to 1665, 1666 to 1675, 1676 to 1685, 1686 to 1695, 1696 to 1705, 1706 to 1715, 1716 to 1725, 1726 to 1735, 1736 to 1745, 1746 to 1755, 1756 to 1765, 1766 to 1775, 1776 to 1785, and/or 1786 to 1795 as depicted in Figures 1A-H (SEQ ID NO:2). Polynucleotides encoding these polypeptides are also encompassed by the invention.

In specific embodiments, polypeptide fragments of the WF-HABP invention comprise, or alternatively consist of, amino acid residues: 1 to 10, 5 to 15, 16 to 25, 26 to 35, 36 to 45, 46 to 55, 56 to 65, 66 to 75, 76 to 85, 86 to 95, 96 to 105, 106 to 115, 116 to 125, 126 to 135, 136 to 145, 146 to 155, 156 to 165, 166 to 175, 176 to 185, 186 to 195, 196 to 205, 206 to 215, and/or 216 to 225 as depicted in Figures 2A-B (SEQ ID NO:5). Polynucleotides encoding these polypeptides are also encompassed by the invention.

In specific embodiments, polypeptide fragments of the OE-HABP invention comprise, or alternatively consist of, amino acid residues: 52 to 60, 61 to 70, 71 to 80, 81 to 90, 91 to 100, 101 to 110, 111 to 120, 200 to 209, 210 to 220, 221 to 230, 231 to 240, 241 to 250, 251 to 260, 261 to 270, 271 to 280, and/or 281 to 290 as depicted in Figures 3A-B (SEQ ID NO:8). Polynucleotides encoding these polypeptides are also encompassed by the invention.

In specific embodiments, polypeptide fragments of the BM-HABP invention comprise, or alternatively consist of, amino acid residues: 1 to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 50, 51 to 60, 61 to 70, 71 to 80, 81 to 88, 200 to 209, 210 to 220, 221 to 230, 231 to 240, 241 to 250, 251 to 260, 261 to 270, 271 to 280, 281 to 290, 291 to 300, 301 to 310, 311 to 320, 321 to 330, 331 to 340, and/or 341 to 350, as depicted in Figures 4A-B (SEQ ID NO:11). Polynucleotides encoding these polypeptides are also encompassed by the invention.

Among the especially preferred fragments of the invention are fragments characterized by structural or functional attributes of WF-HABP, OE-HABP, and BM-HABP. Such fragments include amino acid residues that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet-forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-

forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, surface forming regions, and high antigenic index regions (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) of complete (i.e., full-length) WF-HABP (SEQ ID NO:2), WF-HABP (SEQ ID NO:5), complete (i.e., full-length) OE-HABP (SEQ ID NO:8), and complete (i.e., full-length) BM-HABP (SEQ ID NO:11). Certain preferred regions are those set out in Figures 9, 10, 11, and 12, respectively, and include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence depicted in Figures 1A-1H (SEQ ID NO:2), Figures 2A-2B (SEQ ID NO:5), Figures 3A-3B (SEQ ID NO:8), and Figures 4A-4B (SEQ ID NO:11), and such preferred regions include; Garnier-Robson predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Kyte-Doolittle predicted hydrophilic and hydrophobic regions; Eisenberg alpha and beta amphipathic regions; Emini surface-forming regions; and Jameson-Wolf high antigenic index regions, as predicted using the default parameters of these computer programs. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In additional embodiments, the polynucleotides of the invention encode functional attributes of WF-HABP, OE-HABP, and BM-HABP. Preferred embodiments of the invention in this regard include fragments that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions of WF-HABP, OE-HABP, and BM-HABP.

The data representing the structural or functional attributes of WF-HABP, OE-HABP, and BM-HABP are set forth in Figures 1A-1H, Figures 2A-2B, Figures 3A-3B, and Figures 4A-4B, and/or Tables I-IV, as described above, was generated using the various modules and algorithms of the DNA\*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Tables I-IV can be used to determine regions of WF-HABP, OE-HABP, and BM-HABP which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or IV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

Certain preferred regions of WF-HABP (SEQ ID NO:2) in these regards are set out in Figure 9, but may, as shown in Table I, be represented or identified by using tabular representations of the data presented in Figure 9. Certain preferred regions of WF-HABP (SEQ ID NO:5) in these regards are set out in Figure 10, but may, as shown in Table II, be represented or identified by using tabular representations of the data presented in Figure 10. Certain preferred regions of OE-HABP (SEQ ID NO:8) in these regards are set out in Figure 11, but may, as shown in Table III, be represented or identified by using tabular representations of the data presented in Figure 11. Certain preferred regions of BM-HABP (SEQ ID NO:11) in these regards are set out in Figure 12, but may, as shown in Table IV, be represented or identified by using tabular representations of the data presented in Figure 12. The DNA\*STAR computer algorithm used to generate Figures 9-12 (set on the original default parameters) was used to present the data in Figures 9-12 in a tabular format (See Tables I-IV). The tabular format of the data in Figures 9-12 may be used to easily determine specific boundaries of a preferred region.

The above-mentioned preferred regions set out in Figures 9-12 and in Tables I-IV include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in Figures 1A-1H, 2A-2B, 3A-3B, and 4A-4B, respectively. As set out in Figures 9-12 and in Tables I-IV, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and coil-regions, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions and Jameson-Wolf regions of high antigenic index.

Table I:

	•Res	Pos.I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
5	Met	1	.	.	B	.	.	.	.	0.40	.	.	.	0.99	1.06
	Met	2	.	.	B	.	.	.	.	0.12	*	.	.	1.18	0.82
	Asp	3	.	.	.	.	T	T	.	0.62	*	.	.	1.52	0.34
	Gln	4	.	.	.	.	T	T	.	1.01	*	.	.	2.46	0.68
	Gly	5	.	.	.	.	T	T	.	0.51	*	.	F	3.40	1.19
10	Cys	6	.	.	B	.	.	T	.	0.30	*	.	F	2.51	0.50
	Arg	7	.	.	B	B	.	.	.	0.59	*	.	F	1.47	0.24
	Glu	8	.	.	B	B	.	.	.	0.28	*	.	.	0.98	0.35
	Ile	9	.	.	B	B	.	.	.	-0.31	*	.	.	0.64	0.94
	Leu	10	.	.	B	B	.	.	.	-0.31	*	.	.	0.30	0.48
15	Thr	11	.	.	B	B	.	.	.	0.14	*	.	F	-0.15	0.28
	Thr	12	.	.	.	B	T	.	.	-0.67	*	.	F	-0.05	0.61
	Ala	13	.	.	.	B	.	.	C	-0.98	.	.	F	-0.25	0.64
	Gly	14	.	.	.	.	.	T	C	-0.94	.	.	F	0.15	0.64
	Pro	15	.	.	.	.	.	T	C	-0.94	.	.	F	0.15	0.33
20	Phe	16	.	.	B	.	.	T	.	-1.49	.	.	.	-0.20	0.27
	Thr	17	.	.	B	.	.	T	.	-1.39	.	.	.	-0.20	0.20
	Val	18	.	.	B	B	.	.	.	-1.10	.	.	.	-0.60	0.20
	Leu	19	.	.	B	B	.	.	.	-1.61	.	.	.	-0.60	0.31
	Val	20	.	.	B	B	.	.	.	-1.70	*	.	.	-0.60	0.16
25	Pro	21	.	.	B	B	.	.	.	-1.30	*	.	F	-0.45	0.29
	Ser	22	.	.	B	.	.	T	.	-1.69	.	.	F	-0.05	0.47
	Val	23	.	.	B	.	.	T	.	-1.13	*	.	F	-0.05	0.55
	Ser	24	.	.	B	.	.	T	.	-0.62	*	*	F	-0.05	0.48
	Ser	25	.	.	B	.	.	T	.	0.34	*	*	F	0.25	0.48
30	Phe	26	.	.	B	.	.	.	.	0.24	*	.	F	1.04	1.25
	Ser	27	.	.	B	.	.	T	.	-0.06	*	.	F	1.48	1.35
	Ser	28	.	.	.	.	.	T	C	0.80	*	.	F	1.17	1.00
	Arg	29	.	.	B	.	.	T	.	0.51	*	.	F	1.36	1.85
	Thr	30	.	.	.	.	.	T	C	0.51	*	*	F	2.40	1.40
35	Met	31	.	.	.	.	.	.	C	0.40	.	.	.	1.81	1.40
	Asn	32	.	.	.	.	.	T	C	0.11	*	.	.	1.02	0.59
	Ala	33	.	.	.	.	.	T	C	0.41	.	.	.	0.48	0.41
	Ser	34	.	.	.	.	.	T	C	0.30	*	*	.	0.24	0.72
	Leu	35	.	.	B	.	.	T	.	-0.20	.	*	.	0.10	0.78
40	Ala	36	.	A	B	.	.	.	.	-0.27	*	*	.	-0.60	0.63
	Gln	37	.	A	B	.	.	.	.	-0.16	*	.	.	-0.60	0.25
	Gln	38	.	A	B	.	.	.	.	0.43	*	.	.	-0.30	0.60
	Leu	39	.	A	B	.	.	.	.	0.70	*	*	.	0.45	1.03
	Cys	40	.	A	B	.	.	.	.	0.62	*	.	.	0.30	0.81
45	Arg	41	.	A	B	.	.	.	.	0.32	*	.	.	-0.30	0.33
	Gln	42	.	A	B	.	.	.	.	-0.27	*	.	.	-0.60	0.28
	His	43	.	A	B	.	.	.	.	-0.61	*	.	.	-0.30	0.53
	Ile	44	.	A	B	.	.	.	.	0.20	*	.	.	-0.30	0.27
	Ile	45	.	A	B	.	.	.	.	0.83	*	.	.	-0.60	0.27

100% of the total amino acid content in the protein is accounted for by the following amino acids:

5	Ala	46	.	A	B	.	.	.	.	-0.17	*	.	.	-0.60	0.27
	Gly	47	.	A	B	.	.	.	.	-0.98	.	.	.	-0.60	0.27
	Gln	48	.	A	B	.	.	.	.	-0.94	.	.	.	-0.60	0.31
	His	49	.	A	B	.	.	.	.	-0.06	.	.	.	-0.30	0.54
	Ile	50	.	A	B	.	.	.	.	0.52	*	*	.	0.64	0.90
10	Leu	51	.	A	B	.	.	.	.	1.22	*	.	.	0.98	0.75
	Glu	52	.	A	B	.	.	.	.	1.26	*	*	F	1.92	1.08
	Asp	53	.	.	.	.	T	T	.	1.26	*	.	F	3.06	2.23
	Thr	54	.	.	.	.	T	T	.	1.29	.	*	F	3.40	4.68
	Arg	55	.	.	.	.	T	T	.	1.87	*	.	F	3.06	4.68
15	Thr	56	.	.	.	.	T	T	.	2.79	.	.	F	2.72	4.05
	Gln	57	.	.	.	B	T	.	.	2.90	.	*	F	1.98	5.49
	Gln	58	.	.	.	B	T	.	.	2.61	*	*	F	1.64	5.49
	Thr	59	.	.	.	B	.	.	C	2.63	*	.	F	0.80	4.00
	Arg	60	.	.	.	B	T	.	.	2.21	.	*	F	0.40	2.43
20	Arg	61	.	.	.	B	T	.	.	1.71	*	.	F	0.40	2.03
	Trp	62	.	.	.	B	T	.	.	1.12	*	.	.	-0.05	1.16
	Trp	63	.	.	.	B	.	.	C	0.78	*	.	.	-0.40	0.60
	Thr	64	.	.	.	B	.	.	C	1.09	*	.	.	-0.40	0.30
	Leu	65	.	.	.	B	.	.	C	0.98	*	.	.	-0.40	0.50
25	Ala	66	.	.	.	B	.	.	C	-0.02	*	.	.	-0.40	0.82
	Gly	67	.	.	.	B	.	.	C	-0.04	.	.	F	0.05	0.40
	Gln	68	.	.	.	B	.	.	C	-0.61	.	.	F	0.05	0.70
	Glu	69	.	.	B	B	.	.	.	-0.61	.	*	F	-0.15	0.51
	Ile	70	.	.	B	B	.	.	.	-0.50	.	*	F	-0.15	0.75
30	Thr	71	.	.	B	B	.	.	.	0.09	*	*	.	-0.60	0.37
	Val	72	.	.	B	B	.	.	.	0.43	*	.	.	-0.60	0.35
	Thr	73	.	.	B	B	.	.	.	-0.27	*	*	.	-0.60	0.85
	Phe	74	.	.	B	B	.	.	.	-0.58	*	*	.	-0.60	0.51
	Asn	75	.	.	B	B	.	.	.	0.36	*	*	.	-0.60	1.00
35	Gln	76	.	.	B	B	.	.	.	0.42	*	.	.	-0.15	1.38
	Phe	77	.	.	.	B	T	.	.	0.98	*	.	F	0.10	2.50
	Thr	78	.	.	.	B	T	.	.	1.04	*	*	F	0.40	2.08
	Lys	79	.	.	.	B	T	.	.	1.79	*	*	F	0.10	1.88
	Tyr	80	.	.	.	.	T	T	.	1.54	*	*	.	0.99	4.35
40	Ser	81	.	.	.	.	T	T	.	1.59	*	*	.	1.33	4.73
	Tyr	82	.	.	.	.	T	T	.	2.29	*	*	.	2.27	4.73
	Lys	83	.	.	.	.	T	T	.	2.60	*	*	.	2.61	5.04
	Tyr	84	.	.	.	.	T	T	.	2.34	*	*	F	3.40	6.51
	Lys	85	.	.	.	.	T	T	.	2.59	.	*	F	3.06	6.42
45	Asp	86	.	.	B	.	.	T	.	2.89	.	*	F	2.32	5.56
	Gln	87	.	.	B	.	.	T	.	2.82	*	*	F	1.98	6.15
	Pro	88	.	.	B	.	.	.	.	2.08	*	*	F	1.44	4.44
	Gln	89	.	.	B	B	.	.	.	2.32	*	*	F	0.60	2.30
	Gln	90	.	.	B	B	.	.	.	1.39	*	*	F	0.00	2.14
	Thr	91	.	.	B	B	.	.	.	1.14	*	.	F	-0.45	0.97
	Phe	92	.	.	B	B	.	.	.	1.19	.	*	.	-0.60	0.88
	Asn	93	.	.	B	B	.	.	.	0.81	.	.	.	-0.45	1.01
	Ile	94	.	.	B	B	.	.	.	0.81	.	.	.	-0.60	0.71

5	Tyr	95	.	.	B	.	.	.	.	0.81	.	.	.	-0.25	1.32
	Lys	96	.	.	.	.	.	.	C	0.23	.	.	.	0.25	1.32
	Ala	97	.	.	.	.	.	.	C	0.34	.	.	F	0.10	1.32
	Asn	98	.	.	.	.	.	.	C	-0.24	*	.	.	0.10	0.85
	Asn	99	.	.	B	.	.	.	.	0.64	*	.	.	0.50	0.43
10	Ile	100	.	.	B	.	.	.	.	0.54	*	.	.	-0.10	0.68
	Ala	101	.	.	B	.	.	T	.	-0.36	*	.	.	0.10	0.42
	Ala	102	.	.	B	.	.	T	.	-0.47	.	.	.	-0.20	0.19
	Asn	103	.	.	B	.	.	T	.	-0.50	.	*	.	-0.20	0.24
	Gly	104	.	.	B	.	.	T	.	-1.36	*	*	.	-0.20	0.32
15	Val	105	.	.	B	B	.	.	.	-1.32	*	*	.	-0.60	0.24
	Phe	106	.	.	B	B	.	.	.	-1.04	*	.	.	-0.60	0.11
	His	107	.	.	B	B	.	.	.	-0.80	*	.	.	-0.60	0.16
	Val	108	.	.	B	B	.	.	.	-1.61	*	*	.	-0.60	0.21
	Val	109	.	.	B	B	.	.	.	-1.16	*	*	.	-0.60	0.20
20	Thr	110	.	.	B	B	.	.	.	-0.59	.	*	.	-0.30	0.29
	Gly	111	.	.	B	B	.	.	.	0.11	.	*	.	-0.60	0.41
	Leu	112	.	.	B	B	.	.	.	-0.44	*	*	.	-0.60	0.96
	Arg	113	.	.	.	B	T	.	.	0.20	.	*	.	-0.20	0.67
	Trp	114	.	.	.	B	T	.	.	0.76	.	*	.	0.25	1.05
25	Gln	115	.	.	B	B	.	.	.	0.72	.	*	.	-0.15	1.71
	Ala	116	.	.	B	.	.	T	C	0.76	.	*	F	0.45	0.86
	Pro	117	.	.	.	.	T	T	.	1.36	.	*	F	0.50	1.19
	Ser	118	.	.	.	.	T	T	.	0.90	.	*	F	1.10	1.06
	Gly	119	.	.	.	.	.	T	C	1.19	.	.	F	1.20	1.04
30	Thr	120	.	.	.	.	.	T	C	0.98	.	.	F	2.10	1.12
	Pro	121	.	.	.	.	.	T	C	1.61	.	.	F	2.40	1.29
	Gly	122	.	.	.	.	.	T	C	1.93	.	.	F	3.00	2.61
	Asp	123	.	.	.	.	.	T	C	1.92	*	.	F	2.70	3.55
	Pro	124	.	.	.	.	.	T	C	1.38	*	.	F	2.49	3.31
35	Lys	125	.	.	B	.	.	T	.	1.34	*	.	F	2.08	2.35
	Arg	126	.	.	B	.	.	T	.	1.56	*	.	F	1.87	1.39
	Thr	127	.	.	B	.	.	T	.	1.01	*	.	F	1.66	1.56
	Ile	128	.	.	B	B	.	.	.	0.20	*	.	F	0.90	0.55
	Gly	129	.	.	B	B	.	.	.	-0.18	*	.	F	0.21	0.23
40	Gln	130	.	.	B	B	.	.	.	-0.52	*	.	.	-0.33	0.16
	Ile	131	.	.	B	B	.	.	.	-0.94	*	*	.	-0.42	0.31
	Leu	132	.	.	B	B	.	.	.	-0.63	.	.	.	-0.51	0.45
	Ala	133	.	.	B	B	.	.	.	-0.33	*	.	.	-0.30	0.45
	Ser	134	.	.	B	B	.	.	.	-0.69	.	*	F	-0.15	0.65
45	Thr	135	.	A	.	.	.	.	C	-0.99	*	*	F	0.05	0.68
	Glu	136	.	A	B	.	.	.	.	0.01	*	*	F	-0.15	0.90
	Ala	137	.	A	.	.	.	.	C	0.12	*	*	.	0.65	1.32
	Phe	138	.	A	.	.	.	.	C	0.71	*	*	.	0.50	0.79
	Ser	139	.	A	.	.	.	.	C	0.70	*	*	.	0.80	0.79
	Arg	140	.	A	B	.	.	.	.	0.12	*	*	.	0.45	1.13
	Phe	141	.	A	B	.	.	.	.	-0.69	*	*	.	-0.30	0.91
	Glu	142	.	A	B	.	.	.	.	-0.10	*	*	.	-0.30	0.56
	Thr	143	.	A	B	.	.	.	.	0.60	*	*	.	0.30	0.50

5	Ile	144	A	B	.	.	.	0.23	*	*	.	-0.30	0.92
	Leu	145	A	B	.	.	.	-0.22	*	*	.	0.30	0.29
	Glu	146	A	.	.	T	.	-0.33	*	.	.	0.10	0.20
	Asn	147	.	.	.	T	T	-0.54	.	.	.	0.20	0.23
	Cys	148	.	.	.	T	T	-0.53	.	.	.	0.50	0.43
10	Gly	149	.	.	.	T	T	-0.53	.	.	.	1.10	0.33
	Leu	150	.	.	.	.	T	C	-0.53	.	.	0.00	0.15
	Pro	151	.	B	.	.	.	-0.53	.	.	.	-0.40	0.22
	Ser	152	.	B	.	.	.	-0.88	*	.	.	-0.01	0.38
	Ile	153	.	B	.	.	.	-0.42	*	.	F	0.23	0.45
15	Leu	154	.	B	.	.	.	-0.42	*	.	F	0.32	0.45
	Asp	155	.	B	.	.	.	0.18	*	*	F	0.41	0.34
	Gly	156	.	.	.	.	T	C	-0.31	*	F	0.90	0.74
	Pro	157	.	.	.	.	T	C	-0.32	.	F	0.81	0.78
	Gly	158	.	.	.	.	T	C	-0.29	.	F	1.32	0.67
20	Pro	159	.	B	.	.	T	.	-0.18	.	F	0.13	0.50
	Phe	160	.	B	B	.	.	-0.77	.	*	.	-0.51	0.28
	Thr	161	.	B	B	.	.	-0.63	.	.	.	-0.60	0.29
	Val	162	.	B	B	.	.	-0.72	.	.	.	-0.60	0.29
	Phe	163	.	B	B	.	.	-0.38	.	.	.	-0.60	0.45
25	Ala	164	.	.	.	.	T	C	-0.17	.	F	0.15	0.50
	Pro	165	.	.	.	.	T	C	-0.06	.	F	0.60	1.16
	Ser	166	.	.	.	.	T	C	-0.60	*	F	0.60	1.35
	Asn	167	.	.	.	.	T	C	0.26	*	F	1.05	0.99
	Glu	168	.	.	.	.	.	C	0.66	*	F	1.30	1.07
30	Ala	169	.	B	.	.	.	0.43	*	*	F	1.10	1.07
	Val	170	.	B	.	.	.	0.76	*	.	F	0.65	0.55
	Asp	171	.	B	.	.	.	1.06	*	.	F	1.26	0.62
	Ser	172	.	B	.	.	.	0.71	*	.	F	1.72	1.03
	Leu	173	.	B	.	.	T	.	0.82	*	F	2.23	1.37
35	Arg	174	.	B	.	.	T	.	0.60	*	F	2.54	1.61
	Asp	175	.	.	.	T	T	.	0.57	*	F	3.10	0.99
	Gly	176	.	.	.	T	T	.	0.32	*	F	2.79	0.84
	Arg	177	.	B	B	.	.	-0.19	*	.	F	1.38	0.67
	Leu	178	.	B	B	.	.	-0.08	*	.	.	0.32	0.33
40	Ile	179	.	B	B	.	.	-0.50	*	.	.	-0.29	0.29
	Tyr	180	.	B	B	.	.	-1.09	*	*	.	-0.60	0.21
	Leu	181	.	B	B	.	.	-1.09	*	*	.	-0.60	0.26
	Phe	182	.	B	B	.	.	-2.01	*	*	.	-0.60	0.37
	Thr	183	.	B	B	.	.	-1.50	*	.	.	-0.60	0.19
45	Ala	184	.	.	B	.	.	C	-0.57	*	.	-0.40	0.32
	Gly	185	.	.	B	.	.	C	-1.13	*	.	-0.10	0.73
	Leu	186	A	.	.	.	.	C	-0.32	*	.	-0.10	0.42
	Ser	187	A	.	.	.	.	C	0.38	*	F	0.05	0.72
	Lys	188	A	.	.	.	.	C	-0.12	*	F	0.80	1.25
	Leu	189	A	B	.	.	.	.	-0.39	*	F	0.60	1.25
	Gln	190	.	B	B	.	.	.	0.07	*	F	0.45	0.69
	Glu	191	.	B	B	.	.	.	0.63	*	.	0.60	0.68
	Leu	192	.	B	B	.	.	.	0.90	*	.	-0.15	1.29

5	Val	193	.	B	B	.	.	.	-0.03	*	*	.	0.45	1.01
	Arg	194	.	B	B	.	.	.	0.53	*	*	.	-0.30	0.41
	Tyr	195	.	B	B	.	.	.	0.53	*	*	.	-0.60	0.78
	His	196	.	B	B	.	.	.	0.50	*	*	.	-0.45	1.69
	Ile	197	.	B	B	.	.	.	0.97	*	*	.	-0.45	1.17
10	Tyr	198	.	.	.	T	.	.	1.82	*	*	.	0.00	0.74
	Asn	199	.	.	.	T	T	.	0.90	.	*	.	0.20	0.94
	His	200	.	.	.	T	T	.	0.83	.	*	.	0.35	1.11
	Gly	201	.	.	.	.	T	C	0.01	*	*	.	0.15	1.02
	Gln	202	.	.	.	.	T	C	0.90	*	*	.	0.00	0.47
15	Leu	203	.	B	B	.	.	.	1.19	*	.	.	-0.30	0.60
	Thr	204	.	B	B	.	.	.	0.38	*	*	.	0.45	1.21
	Val	205	.	B	B	.	.	.	-0.48	*	*	.	0.30	0.58
	Glu	206	.	B	B	.	.	.	-0.43	*	*	.	-0.30	0.49
	Lys	207	.	B	B	.	.	.	-0.39	*	*	F	0.62	0.46
20	Leu	208	.	B	B	.	.	.	0.08	*	*	F	1.24	1.23
	Ile	209	.	B	B	.	.	.	0.50	*	*	F	1.26	0.70
	Ser	210	.	.	.	.	T	C	0.47	*	*	F	2.03	0.69
	Lys	211	.	B	.	.	T	.	-0.34	*	*	F	1.70	0.59
	Gly	212	.	B	.	.	T	.	-0.70	*	*	F	1.53	0.69
25	Arg	213	.	B	.	.	T	.	-0.49	.	*	F	1.36	0.74
	Ile	214	.	B	B	.	.	.	-0.19	.	*	.	0.64	0.37
	Leu	215	.	B	B	.	.	.	0.11	*	*	.	-0.43	0.37
	Thr	216	.	B	B	.	.	.	0.07	*	*	.	-0.30	0.31
	Met	217	.	B	B	.	.	.	-0.44	*	*	.	-0.60	0.76
30	Ala	218	.	B	B	.	.	.	-1.37	*	*	.	-0.60	0.68
	Asn	219	.	B	B	.	.	.	-1.07	*	.	.	-0.60	0.39
	Gln	220	.	B	B	.	.	.	-1.11	.	.	.	-0.60	0.40
	Val	221	.	B	B	.	.	.	-0.80	.	*	.	-0.60	0.29
	Leu	222	.	B	B	.	.	.	-1.09	.	*	.	-0.60	0.29
35	Ala	223	.	B	B	.	.	.	-0.80	.	.	.	-0.60	0.12
	Val	224	.	B	B	.	.	.	-0.80	.	*	.	-0.34	0.21
	Asn	225	.	B	B	.	.	.	-0.80	.	*	.	0.22	0.45
	Ile	226	.	B	B	.	.	.	-0.29	*	*	.	1.08	0.77
	Ser	227	.	B	.	.	T	.	0.63	*	*	F	2.04	1.03
40	Glu	228	.	B	.	.	T	.	0.33	*	*	F	2.60	1.25
	Glu	229	.	B	.	.	T	.	0.38	*	*	F	2.34	1.25
	Gly	230	.	B	.	.	T	.	-0.43	*	*	F	1.93	0.77
	Arg	231	.	B	B	.	.	.	0.11	*	*	F	1.27	0.37
	Ile	232	.	B	B	.	.	.	0.20	.	*	.	0.56	0.21
45	Leu	233	.	B	B	.	.	.	0.20	.	*	.	-0.30	0.33
	Leu	234	.	B	B	.	.	.	-0.14	.	*	.	0.30	0.29
	Gly	235	.	.	.	.	T	C	-0.66	.	*	F	0.45	0.41
	Pro	236	.	.	.	.	T	C	-0.98	.	*	F	0.45	0.37
	Glu	237	.	.	.	T	T	.	-0.90	.	.	F	0.65	0.69
	Gly	238	.	.	.	.	T	C	-0.09	*	.	F	0.45	0.57
	Val	239	.	B	.	.	.	.	0.83	*	.	F	0.05	0.64
	Pro	240	.	B	.	.	.	.	0.32	.	.	.	0.50	0.73
	Leu	241	.	B	B	.	.	.	0.53	.	*	.	-0.30	0.55



5	Gln	242	.	.	B	B	.	.	.	-0.32	.	*	.	0.45	1.23
	Arg	243	.	.	B	B	.	.	.	-0.58	.	*	.	0.30	0.59
	Val	244	.	.	B	B	.	.	.	-0.31	.	*	.	0.30	0.71
	Asp	245	.	.	B	B	.	.	.	-0.69	*	*	.	0.30	0.41
	Val	246	.	.	B	B	.	.	.	0.12	*	*	.	0.30	0.21
10	Met	247	.	.	B	B	.	.	.	-0.22	*	*	.	-0.30	0.46
	Ala	248	.	.	B	.	.	T	.	-1.19	*	*	.	0.10	0.27
	Ala	249	.	.	B	.	.	T	.	-1.22	.	*	.	-0.20	0.27
	Asn	250	.	.	B	.	.	T	.	-1.26	.	*	.	-0.20	0.19
	Gly	251	.	.	B	.	.	T	.	-1.00	*	.	.	-0.20	0.26
15	Val	252	.	.	B	B	.	.	.	-1.21	*	.	.	-0.60	0.26
	Ile	253	.	.	B	B	.	.	.	-0.62	*	.	.	-0.60	0.13
	His	254	.	.	B	B	.	.	.	-0.38	*	.	.	-0.60	0.22
	Met	255	.	.	B	B	.	.	.	-1.27	*	.	.	-0.60	0.29
	Leu	256	.	.	B	B	.	.	.	-1.73	*	.	.	-0.60	0.29
20	Asp	257	.	.	B	B	.	.	.	-1.69	*	.	.	-0.60	0.18
	Gly	258	.	.	B	.	.	.	.	-1.01	.	.	.	-0.40	0.15
	Ile	259	.	.	B	.	.	.	.	-1.19	.	.	.	-0.40	0.28
	Leu	260	.	.	B	.	.	.	.	-0.90	.	.	.	-0.10	0.26
	Leu	261	.	.	B	.	.	.	.	-0.98	.	.	.	-0.40	0.38
25	Pro	262	.	.	B	.	.	T	.	-1.79	.	.	F	-0.05	0.38
	Pro	263	.	.	B	.	.	T	.	-1.66	.	.	F	-0.05	0.38
	Thr	264	.	.	B	.	.	T	.	-1.66	.	.	F	-0.05	0.71
	Ile	265	.	.	B	.	.	T	.	-1.66	.	.	.	-0.20	0.32
	Leu	266	.	.	B	.	.	.	.	-1.06	*	.	.	-0.40	0.17
30	Pro	267	.	.	B	.	.	.	.	-0.80	*	.	.	-0.40	0.18
	Ile	268	.	.	B	.	.	.	.	-0.62	*	.	.	-0.40	0.52
	Leu	269	.	.	B	.	.	.	.	-0.98	*	.	.	-0.10	0.86
	Pro	270	.	.	.	.	.	T	C	-0.39	*	.	.	0.90	0.30
	Lys	271	.	.	.	.	T	T	.	0.42	*	.	F	1.55	0.57
35	His	272	.	.	.	.	.	T	C	0.63	.	.	F	2.40	1.20
	Cys	273	.	.	.	.	.	T	C	1.52	.	.	F	3.00	1.34
	Ser	274	A	A	.	.	.	.	.	2.30	*	.	F	2.10	1.16
	Glu	275	A	A	.	.	.	.	.	2.56	*	*	F	1.80	1.16
	Glu	276	A	A	.	.	.	.	.	1.62	*	.	F	1.50	4.34
40	Gln	277	A	A	.	.	.	.	.	0.80	*	.	F	1.20	2.27
	His	278	.	A	B	.	.	.	.	0.88	.	.	F	0.75	0.97
	Lys	279	.	A	B	.	.	.	.	0.83	.	.	.	0.30	0.57
	Ile	280	.	A	B	.	.	.	.	0.53	.	.	.	-0.30	0.32
	Val	281	.	A	B	.	.	.	.	-0.13	.	.	.	-0.30	0.32
45	Ala	282	.	A	.	.	T	.	.	-0.99	.	*	.	0.10	0.09
	Gly	283	.	.	.	.	T	T	.	-0.96	.	.	.	0.20	0.09
	Ser	284	.	.	B	.	.	T	.	-1.67	.	*	.	0.10	0.20
	Cys	285	.	.	B	.	.	T	.	-0.78	.	*	.	0.10	0.11
	Val	286	.	.	B	.	.	T	.	-0.51	.	.	.	0.10	0.19
	Asp	287	.	A	B	.	.	.	.	-0.73	.	.	.	-0.30	0.14
	Cys	288	.	A	B	.	.	.	.	-0.39	.	.	.	-0.30	0.22
	Gln	289	.	A	B	.	.	.	.	-0.40	.	.	.	-0.30	0.48
	Ala	290	.	A	B	.	.	.	.	-0.03	.	.	.	-0.30	0.41

5	Leu	291	.	A	.	.	T	.	.	0.51	.	.	.	-0.05	1.03
	Asn	292	.	.	.	.	T	T	.	-0.16	.	.	F	0.65	0.86
	Thr	293	.	.	.	.	T	T	.	0.30	.	.	F	0.35	0.45
	Ser	294	.	.	.	.	T	T	.	0.09	.	.	F	0.35	0.85
	Thr	295	.	.	.	.	T	T	.	0.68	.	.	F	0.65	0.82
10	Cys	296	.	.	.	.	.	.	C	1.19	.	.	F	0.25	0.91
	Pro	297	.	.	.	.	.	T	C	0.33	*	.	F	0.45	0.91
	Pro	298	.	.	.	.	T	T	.	0.69	.	*	F	0.65	0.47
	Asn	299	.	.	.	.	T	T	.	0.18	.	*	F	1.40	1.75
	Ser	300	.	.	B	.	.	T	.	0.49	.	*	F	0.85	0.94
15	Val	301	.	.	B	B	.	.	.	0.27	.	*	F	0.60	1.01
	Lys	302	.	.	B	B	.	.	.	-0.22	.	*	F	0.45	0.44
	Leu	303	.	.	B	B	.	.	.	-0.22	.	*	.	-0.07	0.28
	Asp	304	.	.	B	B	.	.	.	-0.18	.	*	.	0.16	0.59
	Ile	305	.	.	B	B	.	.	.	0.12	.	*	.	0.99	0.59
20	Phe	306	.	.	B	B	.	.	.	0.31	.	*	.	1.37	1.24
	Pro	307	.	.	B	.	.	T	.	-0.59	.	*	F	2.30	0.40
	Lys	308	.	.	.	.	T	T	.	-0.02	*	*	F	1.57	0.42
	Glu	309	.	.	B	.	.	T	.	-0.91	*	*	.	0.79	0.77
	Cys	310	.	.	B	.	.	T	.	-0.06	*	.	.	0.56	0.35
25	Val	311	.	.	B	B	.	.	.	0.64	*	.	.	-0.07	0.24
	Tyr	312	.	.	B	B	.	.	.	0.64	.	.	.	-0.30	0.23
	Ile	313	.	.	B	B	.	.	.	0.29	.	.	.	-0.60	0.66
	His	314	.	.	B	B	.	.	.	-0.06	.	.	.	-0.45	1.28
	Asp	315	.	.	B	.	.	T	.	-0.20	.	.	F	0.25	0.81
30	Pro	316	.	.	.	.	T	T	.	0.66	.	*	F	0.65	0.95
	Thr	317	.	.	.	.	T	T	.	0.04	.	.	F	1.40	1.12
	Gly	318	.	.	B	.	.	T	.	0.12	.	.	F	0.25	0.50
	Leu	319	.	A	B	.	.	.	.	0.20	*	.	.	-0.60	0.27
	Asn	320	.	A	B	.	.	.	.	0.24	*	.	.	-0.30	0.37
35	Val	321	.	A	B	.	.	.	.	0.11	*	.	.	0.51	0.74
	Leu	322	.	A	B	.	.	.	.	-0.24	*	.	.	0.72	0.89
	Lys	323	.	A	B	.	.	.	.	-0.49	*	.	F	1.08	0.30
	Lys	324	.	A	B	.	T	.	.	0.02	*	.	F	1.69	0.41
	Gly	325	.	.	.	.	T	.	.	-0.22	*	.	F	2.10	0.66
40	Cys	326	.	.	.	.	T	T	.	-0.03	*	.	.	1.94	0.52
	Ala	327	.	.	B	.	.	T	.	0.78	*	.	.	0.73	0.14
	Ser	328	.	.	B	.	.	T	.	0.73	.	.	.	0.22	0.22
	Tyr	329	.	.	B	.	.	T	.	0.38	*	*	.	0.01	0.73
	Cys	330	.	.	.	B	T	.	.	-0.17	.	.	.	-0.05	1.04
45	Asn	331	.	.	.	B	T	.	.	-0.10	*	.	.	-0.20	0.54
	Gln	332	.	.	B	B	.	.	.	0.49	.	.	F	-0.45	0.34
	Thr	333	.	.	B	B	.	.	.	0.79	.	.	F	0.00	1.11
	Ile	334	.	.	B	B	.	.	.	0.69	.	.	.	0.45	1.19
	Met	335	.	.	B	B	.	.	.	0.69	.	.	.	-0.02	0.68
	Glu	336	.	.	B	.	.	T	.	0.02	.	.	F	0.81	0.25
	Gln	337	.	.	B	.	.	T	.	0.07	*	*	F	1.09	0.19
	Gly	338	.	.	.	.	T	T	.	0.03	*	.	F	2.37	0.39
	Cys	339	.	.	.	.	T	T	.	0.22	.	*	.	2.80	0.22

5	Cys	340	.	.	.	T	T	.	0.12	.	.	.	1.62	0.11
	Lys	341	.	.	.	T	T	.	-0.22	.	.	.	1.04	0.10
	Gly	342	.	.	.	T	T	.	-0.43	.	*	.	0.76	0.18
	Phe	343	.	.	.	T	T	.	-0.09	.	*	.	0.48	0.52
	Phe	344	.	.	.	T	.	.	-0.09	.	.	.	0.90	0.43
10	Gly	345	.	.	.	T	T	.	0.27	.	.	F	0.56	0.24
	Pro	346	.	.	.	T	T	.	0.22	.	.	F	0.77	0.39
	Asp	347	.	.	.	T	T	.	-0.10	.	.	F	1.28	0.78
	Cys	348	.	.	.	T	T	.	0.39	.	.	F	2.09	0.43
	Thr	349	.	.	.	T	.	.	0.74	.	.	F	2.10	0.43
15	Gln	350	.	B	.	.	.	.	0.74	.	.	F	1.49	0.25
	Cys	351	.	B	.	.	T	.	0.26	.	.	F	0.88	0.47
	Pro	352	.	.	.	T	T	.	-0.04	.	.	F	0.77	0.28
	Gly	353	.	.	.	T	T	.	0.62	.	.	F	0.56	0.22
	Gly	354	.	.	.	T	T	.	0.72	.	.	F	0.35	0.65
20	Phe	355	.	.	.	T	.	.	0.06	.	.	F	0.45	0.65
	Ser	356	.	B	.	.	.	.	0.48	.	.	F	-0.25	0.35
	Asn	357	.	B	.	.	T	.	0.34	.	.	F	-0.05	0.56
	Pro	358	.	B	.	.	T	.	0.73	.	.	F	-0.05	0.63
	Cys	359	.	.	.	T	T	.	0.73	.	*	F	1.25	0.95
25	Tyr	360	.	.	.	T	T	.	1.43	.	*	F	0.96	0.58
	Gly	361	.	.	.	T	T	.	1.07	.	*	F	1.27	0.61
	Lys	362	.	.	.	T	T	.	0.77	.	.	F	1.58	0.61
	Gly	363	.	.	.	T	T	.	0.98	.	*	F	2.49	0.52
	Asn	364	.	.	.	T	T	.	1.30	.	*	F	3.10	0.88
30	Cys	365	.	B	.	.	T	.	0.66	.	*	F	2.39	0.43
	Ser	366	.	B	.	.	T	.	1.00	.	*	F	1.95	0.31
	Asp	367	.	B	.	.	T	.	0.61	.	*	F	1.81	0.33
	Gly	368	.	B	.	.	T	.	0.96	.	*	F	1.67	0.61
	Ile	369	.	.	.	T	.	.	0.61	.	*	F	1.73	0.73
35	Gln	370	.	B	.	.	T	.	0.69	.	*	F	1.70	0.43
	Gly	371	.	.	.	T	T	.	0.32	.	.	F	1.33	0.44
	Asn	372	.	.	.	T	T	.	-0.49	.	.	F	0.86	0.34
	Gly	373	.	.	.	T	T	.	-0.81	.	*	F	0.69	0.16
	Ala	374	.	B	.	.	.	.	-0.62	.	*	.	-0.23	0.09
40	Cys	375	.	B	.	.	.	.	-0.83	.	.	.	-0.40	0.05
	Leu	376	.	B	.	.	.	.	-0.49	.	.	.	-0.40	0.07
	Cys	377	.	B	.	.	.	.	-0.73	.	.	.	-0.40	0.12
	Phe	378	.	B	.	.	T	.	-0.34	.	.	.	0.01	0.36
	Pro	379	.	.	.	T	T	.	-0.10	.	.	F	1.07	0.86
45	Asp	380	.	.	.	T	T	.	-0.32	.	.	F	2.03	1.59
	Tyr	381	.	.	.	T	T	.	-0.10	.	.	F	1.64	1.29
	Lys	382	.	.	.	T	.	.	-0.10	.	.	F	2.10	0.84
	Gly	383	.	.	B	T	.	.	0.57	*	.	.	1.54	0.27
	Ile	384	.	B	B	.	.	.	-0.11	*	.	.	0.03	0.23
	Ala	385	.	B	B	.	.	.	-0.78	*	.	.	0.12	0.08
	Cys	386	.	B	B	.	.	.	-0.83	*	.	.	-0.39	0.04
	His	387	.	B	B	.	.	.	-0.88	*	.	.	-0.60	0.09
	Ile	388	.	B	B	.	.	.	-0.74	.	*	.	-0.60	0.14

	Cys	389	.	.	B	T	.	.	0.14	*	*	.	-0.20	0.39
	Ser	390	.	.	B	T	.	.	0.78	*	.	F	0.59	0.46
	Asn	391	.	.	.	.	T	C	1.41	*	.	F	1.88	1.32
	Pro	392	.	.	.	T	T	.	1.10	*	.	F	2.42	3.34
5	Asn	393	.	.	.	T	T	.	1.99	*	.	F	2.76	2.47
	Lys	394	.	.	.	T	T	.	2.66	*	.	F	3.40	2.66
	His	395	A	.	.	T	.	.	2.29	*	.	F	2.66	2.98
	Gly	396	A	.	.	T	.	.	2.29	*	.	F	2.17	0.99
	Glu	397	A	.	.	T	.	.	2.50	*	.	F	1.83	0.86
10	Gln	398	A	B	.	.	.	.	2.50	*	.	F	1.49	1.09
	Cys	399	A	B	.	.	.	.	1.79	*	.	F	1.40	1.85
	Gln	400	A	.	.	T	.	.	1.48	.	.	F	1.90	0.57
	Glu	401	A	.	.	T	.	.	1.16	.	.	F	2.15	0.33
	Asp	402	.	.	.	T	T	.	0.30	.	.	F	2.50	0.33
15	Cys	403	.	.	.	T	T	.	0.27	.	.	.	2.10	0.14
	Gly	404	.	.	.	T	T	.	0.59	.	.	.	1.85	0.11
	Cys	405	.	.	.	T	T	.	-0.22	.	.	.	1.00	0.07
	Val	406	.	B	B	.	.	.	-0.89	.	.	.	-0.35	0.10
	His	407	.	B	B	.	.	.	-0.89	.	.	.	-0.60	0.05
20	Gly	408	.	B	B	.	.	.	-0.22	.	*	.	-0.60	0.17
	Leu	409	.	B	.	.	.	.	0.23	.	*	.	-0.10	0.37
	Cys	410	.	B	.	.	.	.	0.69	.	*	.	0.84	0.53
	Asp	411	.	.	.	T	.	.	1.20	.	*	F	1.73	0.82
	Asn	412	.	.	.	T	.	.	0.93	.	.	F	2.07	0.99
25	Arg	413	.	.	.	.	T	C	0.93	.	.	F	2.86	2.47
	Pro	414	.	.	.	T	T	.	1.40	.	.	F	3.40	1.47
	Gly	415	.	.	.	T	T	.	1.21	.	.	F	2.61	0.90
	Ser	416	.	.	.	T	T	.	0.54	.	.	F	2.27	0.34
	Gly	417	.	.	.	T	.	.	0.54	.	.	F	1.13	0.12
30	Gly	418	.	B	.	.	.	.	0.43	*	.	F	0.39	0.21
	Val	419	.	B	.	.	.	.	0.30	.	.	F	0.05	0.27
	Cys	420	.	B	.	.	.	.	0.33	.	.	F	0.05	0.27
	Gln	421	.	B	.	.	T	.	-0.03	.	.	F	0.25	0.39
	Gln	422	.	B	.	.	T	.	-0.28	.	.	F	-0.05	0.28
35	Gly	423	.	B	.	.	T	.	-0.14	.	.	F	0.25	0.53
	Thr	424	.	B	.	.	T	.	0.37	.	.	F	0.25	0.47
	Cys	425	.	B	.	.	.	.	0.33	.	.	F	0.05	0.27
	Ala	426	.	B	.	.	T	.	0.03	.	.	.	-0.20	0.24
	Pro	427	.	.	.	T	T	.	-0.31	.	*	F	0.35	0.22
40	Gly	428	.	.	.	T	T	.	0.14	*	*	F	0.35	0.41
	Phe	429	.	.	.	T	T	.	-0.24	.	*	F	1.25	0.79
	Ser	430	.	.	.	T	.	.	-0.24	*	*	F	0.45	0.44
	Gly	431	.	.	.	T	T	.	0.34	*	*	F	0.65	0.24
	Arg	432	.	B	.	.	T	.	0.56	*	*	F	0.25	0.44
45	Phe	433	.	.	.	T	T	.	0.60	*	*	.	1.44	0.57
	Cys	434	.	.	.	T	T	.	0.70	*	*	.	1.78	0.78
	Asn	435	.	.	.	T	.	.	0.66	*	*	.	1.92	0.39
	Glu	436	.	.	.	T	.	.	1.00	*	*	F	1.81	0.45
	Ser	437	.	.	.	T	T	.	0.22	*	*	F	3.40	1.40

5	Met	438	.	.	.	T	T	.	0.58	.	.	F	2.91	0.47
	Gly	439	.	.	.	T	T	.	1.03	.	.	F	2.70	0.27
	Asp	440	.	.	.	T	T	.	0.72	.	.	F	2.19	0.31
	Cys	441	.	.	.	T	.	.	0.38	*	.	F	1.78	0.45
	Gly	442	.	.	.	.	T	C	-0.13	.	.	F	1.57	0.45
	Pro	443	.	.	.	T	T	.	-0.12	*	.	F	1.30	0.22
	Thr	444	.	.	.	T	T	.	0.22	.	.	F	0.87	0.42
10	Gly	445	.	.	.	T	T	.	0.19	.	.	F	1.04	0.73
	Leu	446	.	A	B	.	.	.	0.19	.	.	.	-0.34	0.64
	Ala	447	.	A	B	.	.	.	0.50	.	.	.	-0.47	0.24
	Gln	448	.	A	B	.	.	.	-0.10	.	.	.	-0.60	0.33
	His	449	.	A	B	.	.	.	0.18	.	.	.	-0.60	0.33
	Cys	450	.	A	B	.	.	.	-0.07	*	*	.	-0.60	0.44
	His	451	.	A	B	.	.	.	0.86	*	*	.	-0.60	0.26
15	Leu	452	.	A	B	.	.	.	0.78	*	*	.	-0.30	0.37
	His	453	.	A	.	.	T	.	-0.08	*	*	.	0.10	0.37
	Ala	454	.	A	.	.	T	.	-0.34	*	*	.	-0.20	0.20
	Arg	455	.	A	.	.	T	.	0.32	*	*	.	0.10	0.33
	Cys	456	.	A	B	.	.	.	0.36	*	*	.	-0.30	0.42
	Val	457	.	A	B	.	.	.	0.82	.	*	.	0.61	0.72
	Ser	458	.	.	B	.	.	T	0.00	*	*	F	1.77	0.36
20	Gln	459	.	.	.	T	T	.	0.00	.	*	F	1.58	0.50
	Glu	460	.	.	.	T	T	.	0.00	.	*	F	1.89	0.68
	Gly	461	.	.	.	T	T	.	0.00	.	*	F	3.10	1.00
	Val	462	.	.	.	T	.	.	0.97	.	*	.	2.14	0.31
	Ala	463	.	.	B	.	.	.	0.60	.	*	.	1.73	0.35
	Arg	464	.	.	B	.	.	.	-0.21	.	*	.	1.12	0.19
	Cys	465	.	.	B	.	.	.	-0.21	.	*	.	1.09	0.21
30	Arg	466	.	.	B	.	.	.	-0.21	.	*	.	1.36	0.35
	Cys	467	.	.	B	.	.	T	-0.06	.	*	.	1.84	0.18
	Leu	468	.	.	B	.	.	T	0.53	.	*	.	1.22	0.28
	Asp	469	.	.	.	.	T	T	0.08	.	*	.	2.80	0.25
	Gly	470	.	.	.	.	T	T	0.74	*	*	F	2.37	0.46
	Phe	471	.	.	.	.	T	.	0.29	*	.	F	2.44	0.94
	Glu	472	.	.	.	.	T	.	0.26	.	.	F	2.41	0.56
35	Gly	473	.	.	.	.	T	T	0.77	.	.	F	2.28	0.49
	Asp	474	.	.	.	.	T	T	0.10	.	.	F	2.25	0.75
	Gly	475	.	.	.	.	T	T	0.13	.	.	F	2.50	0.23
	Phe	476	.	.	.	.	T	T	0.62	.	.	.	1.50	0.34
	Ser	477	.	.	.	.	T	.	0.32	.	.	.	1.05	0.31
	Cys	478	.	.	.	.	T	.	0.67	.	.	.	0.50	0.43
	Thr	479	.	.	.	.	.	.	C	0.46	.	F	0.20	0.79
40	Pro	480	.	.	.	.	T	.	0.13	.	.	F	0.45	0.91
	Ser	481	.	.	.	.	T	.	0.53	.	.	F	0.45	0.91
	Asn	482	.	.	.	.	.	T	C	0.80	.	F	0.45	0.85
	Pro	483	.	.	.	.	T	T	1.26	.	.	F	0.65	0.75
	Cys	484	.	.	.	.	T	T	1.57	*	.	F	0.99	0.86
	Ser	485	.	.	B	.	T	T	1.89	*	.	F	1.93	0.89
	His	486	.	.	B	.	.	T	1.84	*	.	F	2.32	1.13

5	Pro	487	.	B	.	.	T	.	1.50	*	.	F	2.66	2.09
	Asp	488	.	.	.	T	T	.	1.04	*	.	F	3.40	1.55
	Arg	489	.	.	.	T	T	.	1.41	*	.	F	2.91	0.61
	Gly	490	.	.	.	T	.	.	1.71	.	.	F	2.68	0.53
	Gly	491	.	.	.	T	.	.	1.74	.	.	F	2.65	0.55
	Cys	492	.	.	.	T	T	.	1.37	.	*	F	2.82	0.45
	Ser	493	.	.	.	.	T	C	1.37	.	*	F	2.29	0.46
	Glu	494	.	.	.	T	T	.	0.59	.	*	F	3.10	0.80
10	Asn	495	.	B	.	.	T	.	0.08	.	.	F	2.39	0.80
	Ala	496	.	B	.	.	.	.	0.21	.	.	.	1.43	0.44
	Glu	497	.	B	.	.	.	.	0.53	.	.	.	1.12	0.40
	Cys	498	.	B	.	.	.	.	0.53	*	.	.	0.81	0.24
15	Val	499	.	B	.	.	T	.	-0.28	*	.	.	0.70	0.32
	Pro	500	.	.	.	T	T	.	-0.62	.	.	F	0.65	0.15
	Gly	501	.	.	.	T	T	.	-0.34	.	.	F	0.35	0.28
	Ser	502	.	.	.	T	T	.	-0.38	.	.	F	0.35	0.55
	Leu	503	.	.	.	T	.	.	0.26	.	.	F	0.45	0.49
	Gly	504	.	.	.	T	.	.	0.44	.	.	F	0.15	0.67
	Thr	505	.	.	.	T	.	.	0.34	.	.	.	0.00	0.27
	His	506	.	B	.	.	.	.	0.02	.	.	.	-0.40	0.47
20	His	507	.	B	.	.	.	.	0.29	.	.	.	-0.40	0.25
	Cys	508	.	B	.	.	.	.	1.14	.	.	.	-0.40	0.24
	Thr	509	.	B	.	.	.	.	1.14	.	.	.	-0.10	0.35
	Cys	510	.	.	.	T	.	.	1.17	.	.	.	0.30	0.26
25	His	511	.	.	.	T	T	.	0.90	.	.	.	0.20	0.50
	Lys	512	.	.	.	T	T	.	0.59	.	.	.	0.50	0.47
	Gly	513	.	.	.	T	T	.	1.26	.	.	F	0.65	0.86
	Trp	514	.	.	.	T	T	.	1.22	*	*	F	1.71	1.06
30	Ser	515	.	.	.	T	T	.	2.00	*	*	F	1.87	0.52
	Gly	516	.	.	.	T	T	.	1.18	*	*	F	2.33	1.03
	Asp	517	.	.	.	T	T	.	0.47	*	*	F	2.49	0.73
	Gly	518	.	.	.	T	T	.	-0.04	.	*	F	3.10	0.29
35	Arg	519	.	B	B	.	.	.	-0.34	*	*	F	1.69	0.22
	Val	520	.	B	B	.	.	.	-0.93	.	*	.	1.23	0.13
	Cys	521	.	B	B	.	.	.	-0.59	*	*	.	0.02	0.09
	Val	522	.	B	B	.	.	.	-0.59	*	*	.	0.01	0.08
	Ala	523	.	B	B	.	.	.	-0.91	*	*	.	-0.30	0.19
	Ile	524	.	B	B	.	.	.	-1.02	.	*	.	0.30	0.19
40	Asp	525	.	B	B	.	.	.	-0.98	.	*	.	0.60	0.44
	Glu	526	.	A	B	.	.	.	-0.31	.	*	.	0.60	0.36
	Cys	527	.	A	B	.	.	.	-0.31	*	*	.	0.91	0.85
	Glu	528	.	A	B	.	.	.	0.39	*	*	.	1.22	0.38
45	Leu	529	.	A	B	.	.	.	0.93	*	*	.	1.53	0.43
	Asp	530	.	A	.	.	.	.	0.59	*	*	.	2.24	0.79
	Val	531	.	.	.	T	T	.	-0.08	.	*	F	3.10	0.45
	Arg	532	.	.	.	T	T	.	0.56	.	*	F	2.49	0.29
	Gly	533	.	.	.	T	T	.	0.24	.	*	F	2.18	0.24
	Gly	534	.	.	.	T	T	.	1.06	.	*	F	1.27	0.46
	Cys	535	.	.	.	T	.	.	0.47	.	*	.	1.51	0.39

5	His	536	.	A	B	.	.	.	.	0.51	.	*	.	0.30	0.40
	Thr	537	.	A	B	.	.	.	.	-0.27	.	*	.	-0.30	0.34
	Asp	538	.	A	B	.	.	.	.	-0.22	.	.	.	-0.30	0.34
	Ala	539	.	A	B	.	.	.	.	-0.12	.	.	.	-0.30	0.33
	Leu	540	.	.	B	B	.	.	.	-0.31	.	.	.	-0.30	0.36
10	Cys	541	.	.	B	B	.	.	.	-0.62	.	.	.	-0.60	0.16
	Ser	542	.	.	B	B	.	.	.	-0.52	*	.	.	-0.60	0.16
	Tyr	543	.	.	B	B	.	.	.	-0.87	*	.	.	-0.60	0.29
	Val	544	.	.	B	B	.	.	.	-0.28	.	.	.	-0.35	0.54
	Gly	545	.	.	.	.	.	T	C	0.23	*	.	*	0.65	0.70
15	Pro	546	.	.	.	.	.	T	.	1.01	.	*	F	1.10	0.60
	Gly	547	.	.	.	.	.	T	.	0.64	.	*	F	2.40	1.58
	Gln	548	.	.	.	.	.	T	.	0.58	.	*	F	2.50	0.85
	Ser	549	.	.	B	.	.	.	.	0.77	*	*	F	1.65	0.80
	Arg	550	.	.	B	.	.	.	.	1.16	*	*	F	1.40	0.43
20	Cys	551	.	.	B	.	.	.	T	0.56	*	*	F	1.65	0.50
	Thr	552	.	.	B	.	.	.	T	0.56	.	*	.	0.95	0.31
	Cys	553	.	.	B	.	.	.	T	-0.14	.	*	.	0.70	0.16
	Lys	554	.	.	B	.	.	.	T	-0.43	*	*	.	-0.20	0.25
	Leu	555	.	.	B	.	.	.	.	-0.89	*	*	.	-0.40	0.18
25	Gly	556	.	.	B	.	.	.	.	-0.22	.	*	.	-0.10	0.32
	Phe	557	.	.	B	.	.	.	.	-0.26	.	*	.	0.50	0.27
	Ala	558	.	.	.	.	.	T	.	0.17	.	*	.	0.30	0.32
	Gly	559	.	.	.	.	.	T	T	0.12	.	*	.	0.50	0.51
	Asp	560	.	.	.	.	.	T	T	0.27	.	.	.	0.65	1.03
30	Gly	561	.	.	.	.	.	T	T	0.31	.	.	.	0.50	0.55
	Tyr	562	.	.	.	.	.	T	T	0.80	.	.	.	1.10	0.74
	Gln	563	.	.	.	.	.	T	.	0.50	.	.	.	0.90	0.68
	Cys	564	.	.	B	.	.	.	.	0.84	.	.	.	-0.17	0.48
	Ser	565	.	.	B	.	.	.	.	0.63	.	.	F	0.51	0.52
35	Pro	566	.	.	B	.	.	.	.	0.31	.	.	F	1.34	0.46
	Ile	567	.	.	B	.	.	.	.	0.67	.	.	F	0.97	0.46
	Asp	568	.	.	B	.	.	.	T	0.08	.	.	F	2.30	0.67
	Pro	569	.	.	B	.	.	.	T	0.40	*	.	F	1.77	0.44
	Cys	570	.	.	B	.	.	.	T	0.70	.	.	F	1.79	0.62
40	Arg	571	.	.	B	.	.	.	T	0.57	*	.	F	2.11	0.60
	Ala	572	.	.	.	.	.	T	.	1.11	*	.	F	2.03	0.38
	Gly	573	.	.	.	.	.	T	.	0.44	*	.	F	2.05	0.71
	Asn	574	.	.	.	.	.	T	T	0.62	*	.	F	2.50	0.19
	Gly	575	.	.	.	.	.	T	T	0.94	*	.	F	1.65	0.26
45	Gly	576	.	.	.	.	.	T	T	0.02	*	.	F	1.40	0.26
	Cys	577	.	.	.	.	.	.	T	0.61	*	.	.	0.50	0.13
	His	578	.	A	B	.	.	.	.	0.14	.	*	.	-0.05	0.23
	Gly	579	.	A	B	.	.	.	.	0.14	.	*	.	-0.30	0.19
	Leu	580	.	A	B	.	.	.	.	-0.10	.	*	.	0.30	0.63
45	Glu	581	.	A	B	.	.	.	.	0.24	.	*	.	0.30	0.47
	Leu	582	A	A	.	.	.	.	.	0.32	.	*	.	0.30	0.76
	Glu	583	A	A	.	.	.	.	.	0.32	.	*	.	0.30	0.93
	Ala	584	A	A	.	.	.	.	.	-0.03	.	*	.	0.30	0.73

5	Asn	585	A	A	.	.	.	.	0.48	.	*	.	-0.30	0.77
	Ala	586	A	A	.	.	.	.	-0.41	.	*	.	-0.30	0.59
	His	587	A	A	.	B	.	.	-0.30	.	*	.	-0.60	0.41
	Phe	588	.	A	B	B	.	.	-0.54	.	*	.	-0.60	0.22
	Ser	589	.	A	B	B	.	.	0.04	*	*	.	-0.60	0.34
10	Ile	590	.	.	B	B	.	.	-0.24	*	*	.	-0.60	0.44
	Phe	591	.	.	B	B	.	.	-0.47	*	*	.	-0.60	0.53
	Tyr	592	.	.	B	B	.	.	-0.39	*	*	.	-0.60	0.33
	Gln	593	.	.	.	B	T	.	0.01	*	.	.	-0.20	0.93
	Trp	594	.	.	.	B	T	.	-0.28	*	.	.	-0.05	1.45
15	Leu	595	.	.	.	B	.	C	0.27	*	.	.	-0.40	0.93
	Lys	596	.	.	.	B	T	.	0.08	*	.	F	0.25	0.53
	Ser	597	.	.	.	.	T	.	0.01	*	.	F	0.15	0.36
	Ala	598	.	.	.	.	T	.	-0.80	*	.	F	0.45	0.62
	Gly	599	.	.	.	.	T	.	-0.72	.	.	.	0.30	0.26
20	Ile	600	.	.	B	.	.	.	-0.50	.	*	.	-0.40	0.30
	Thr	601	.	.	B	.	.	.	-0.54	.	.	.	-0.14	0.30
	Leu	602	.	.	B	.	.	.	-0.13	.	*	.	0.42	0.50
	Pro	603	.	.	B	.	T	.	0.57	*	*	.	1.63	1.39
	Ala	604	.	.	B	.	T	.	0.06	*	*	F	2.34	1.89
25	Asp	605	.	.	B	.	T	.	0.63	*	*	F	2.60	1.70
	Arg	606	.	.	B	.	T	.	0.36	*	*	F	2.34	1.59
	Arg	607	.	.	B	B	.	.	0.36	*	*	F	1.68	1.59
	Val	608	.	.	B	B	.	.	-0.29	*	*	.	1.12	0.78
	Thr	609	.	.	B	B	.	.	0.09	*	*	.	0.56	0.30
30	Ala	610	.	.	B	B	.	.	-0.21	*	*	.	-0.30	0.23
	Leu	611	.	.	B	B	.	.	-0.32	*	*	.	-0.60	0.42
	Val	612	.	.	B	.	.	T	-1.02	*	*	.	0.10	0.51
	Pro	613	.	.	.	.	T	C	-0.76	.	.	F	0.45	0.51
	Ser	614	.	.	.	.	T	C	-1.30	*	*	F	0.45	0.62
35	Glu	615	.	.	B	.	T	.	-0.60	*	*	F	0.25	0.62
	Ala	616	.	A	B	.	.	.	0.21	*	.	.	0.60	0.79
	Ala	617	.	A	B	.	.	.	0.26	*	*	.	0.75	1.02
	Val	618	.	A	B	.	.	.	0.17	*	.	.	0.30	0.49
	Arg	619	.	A	B	.	.	.	0.26	*	.	.	-0.30	0.64
40	Gln	620	.	A	B	.	.	.	0.26	*	.	.	0.04	0.99
	Leu	621	.	A	B	.	.	.	0.84	*	*	F	1.28	2.30
	Ser	622	.	.	.	.	T	C	1.54	*	*	F	2.52	1.96
	Pro	623	.	.	.	.	T	C	1.81	*	.	F	2.86	2.22
	Glu	624	.	.	.	.	T	T	1.00	*	*	F	3.40	2.72
45	Asp	625	.	.	.	.	T	T	0.71	.	*	F	3.06	1.76
	Arg	626	.	A	.	.	T	.	0.71	.	*	.	1.87	1.19
	Ala	627	.	A	B	.	.	.	1.01	.	.	.	0.98	0.57
	Phe	628	.	A	B	.	.	.	1.01	*	*	.	0.04	0.59
	Trp	629	.	A	B	.	.	.	1.12	*	*	.	-0.60	0.47
	Leu	630	.	A	B	.	.	.	0.81	*	.	.	-0.60	0.90
	Gln	631	.	.	B	.	.	T	-0.11	*	*	.	0.07	1.50
	Pro	632	.	.	.	.	T	T	0.27	*	*	F	0.74	1.18
	Arg	633	.	.	.	.	T	T	0.97	*	*	F	1.16	2.21



5	Thr	634	.	.	.	.	T	C	0.44	*	*	F	1.68	2.05
	Leu	635	.	.	.	.	T	C	0.40	*	*	F	1.20	1.10
	Pro	636	.	.	.	.	T	C	0.51	*	*	F	0.93	0.42
	Asn	637	.	.	B	.	T	.	0.13	*	*	.	0.46	0.56
	Leu	638	.	.	B	.	T	.	-0.01	*	*	.	0.34	0.69
10	Val	639	.	A	B	.	.	.	-0.40	*	*	.	-0.18	0.61
	Arg	640	.	A	B	.	.	.	-0.40	*	*	.	-0.60	0.33
	Ala	641	.	A	B	.	.	.	-0.19	.	.	.	-0.60	0.33
	His	642	.	A	B	.	.	.	-0.53	.	.	.	-0.60	0.76
	Phe	643	.	A	B	.	.	.	-0.31	.	*	.	-0.30	0.39
15	Leu	644	.	A	B	.	.	.	-0.27	.	*	.	-0.60	0.39
	Gln	645	.	A	.	.	.	C	-1.08	.	*	.	-0.40	0.23
	Gly	646	.	A	.	.	.	C	-0.49	.	.	.	-0.40	0.23
	Ala	647	.	A	.	.	.	C	-0.46	.	.	.	-0.40	0.49
	Leu	648	.	A	.	.	.	C	0.24	.	.	.	0.50	0.49
20	Phe	649	A	A	.	.	.	.	0.24	.	.	.	0.60	0.86
	Glu	650	A	A	.	.	.	.	-0.34	*	.	.	0.30	0.70
	Glu	651	A	A	.	.	.	.	0.11	*	.	F	0.45	0.86
	Glu	652	A	A	.	.	.	.	-0.11	*	.	F	0.90	1.94
	Leu	653	A	A	.	.	.	.	0.36	*	.	.	0.60	0.93
25	Ala	654	A	A	.	.	.	.	0.71	*	*	.	0.81	0.53
	Arg	655	A	A	.	.	.	.	0.71	*	*	.	0.72	0.30
	Leu	656	.	.	.	.	T	C	0.71	*	*	.	0.93	0.63
	Gly	657	.	.	.	.	T	C	-0.14	*	.	F	2.34	1.09
	Gly	658	.	.	.	.	T	C	0.08	*	*	F	2.10	0.41
30	Gln	659	.	.	B	.	T	.	0.36	*	*	F	1.09	0.50
	Glu	660	.	A	B	.	.	.	-0.57	*	*	F	1.08	0.74
	Val	661	.	A	B	.	.	.	0.24	.	.	.	0.12	0.61
	Ala	662	.	A	B	.	.	.	0.38	.	.	.	-0.09	0.57
	Thr	663	.	A	B	.	.	.	0.41	.	.	.	-0.30	0.51
35	Leu	664	.	.	B	.	.	.	0.10	*	*	.	-0.40	0.99
	Asn	665	.	.	.	.	T	C	0.21	.	*	F	0.30	1.41
	Pro	666	.	.	.	.	T	C	0.78	.	*	F	1.20	1.92
	Thr	667	.	.	.	.	T	C	1.37	.	*	F	0.60	2.45
	Thr	668	.	.	.	.	T	C	0.79	*	*	F	1.20	2.63
40	Arg	669	.	.	B	B	.	.	1.71	*	*	F	0.60	1.19
	Trp	670	.	.	B	B	.	.	1.71	*	*	.	0.70	1.62
	Glu	671	.	.	B	B	.	.	1.03	*	*	.	1.25	1.81
	Ile	672	.	.	B	B	.	.	1.04	*	*	.	1.05	0.65
	Arg	673	.	.	B	B	.	.	1.01	*	*	.	0.70	0.82
45	Asn	674	.	.	.	.	T	T	1.01	*	*	F	2.50	0.47
	Ile	675	.	.	.	.	T	T	0.44	*	*	F	2.40	1.31
	Ser	676	.	.	.	.	.	T	C	0.16	*	F	1.80	0.50
	Gly	677	.	.	.	.	T	T	0.19	*	*	F	0.85	0.33
	Arg	678	.	.	B	B	.	.	0.08	.	*	.	-0.35	0.34
	Val	679	.	.	B	B	.	.	0.08	*	*	.	-0.60	0.45
	Trp	680	.	.	B	B	.	.	0.38	*	*	.	-0.60	0.72
	Val	681	.	.	B	B	.	.	0.38	*	*	.	-0.60	0.37
	Gln	682	.	.	B	B	.	.	-0.13	.	*	.	-0.60	0.67

5	Asn	683	.	B	.	.	T	.	-0.24	.	*	.	-0.20	0.48
	Ala	684	.	B	.	.	T	.	-0.24	.	*	.	0.85	1.07
	Ser	685	.	B	.	.	T	.	-0.54	*	.	.	0.70	0.46
	Val	686	.	B	.	.	T	.	0.31	*	.	.	0.10	0.29
	Asp	687	.	A	B	.	.	.	-0.50	*	.	.	0.30	0.48
10	Val	688	.	A	B	.	.	.	-1.31	*	*	.	0.30	0.29
	Ala	689	.	A	B	.	.	.	-1.31	*	.	.	-0.30	0.33
	Asp	690	.	A	B	.	.	.	-1.32	.	.	.	-0.30	0.20
	Leu	691	.	A	B	.	.	.	-0.47	*	.	.	-0.60	0.38
	Leu	692	.	A	B	.	.	.	-0.81	*	.	.	-0.30	0.61
15	Ala	693	.	B	.	.	T	.	-0.81	.	.	.	0.10	0.36
	Thr	694	.	B	.	.	T	.	-1.03	.	.	F	-0.05	0.33
	Asn	695	.	B	.	.	T	.	-1.07	.	*	F	-0.05	0.33
	Gly	696	.	B	.	.	T	.	-1.14	.	.	F	-0.05	0.44
	Val	697	.	B	B	.	.	.	-1.14	*	.	.	-0.60	0.21
20	Leu	698	.	B	B	.	.	.	-0.86	*	.	.	-0.60	0.11
	His	699	.	B	B	.	.	.	-0.54	*	*	.	-0.60	0.15
	Ile	700	.	B	B	.	.	.	-1.40	*	.	.	-0.60	0.35
	Leu	701	.	B	B	.	.	.	-1.87	*	.	.	-0.60	0.31
	Ser	702	.	B	B	.	.	.	-1.82	*	.	.	-0.60	0.19
25	Gln	703	.	B	B	.	.	.	-1.22	*	*	.	-0.60	0.22
	Val	704	.	B	B	.	.	.	-1.40	*	*	.	-0.60	0.42
	Leu	705	.	B	B	.	.	.	-0.40	*	*	.	-0.60	0.48
	Leu	706	.	B	B	.	.	.	0.07	.	*	.	0.04	0.54
	Pro	707	.	B	.	.	T	.	0.37	.	*	F	0.93	0.72
30	Pro	708	.	.	.	T	T	.	-0.49	.	*	F	2.42	1.46
	Arg	709	.	.	.	T	T	.	0.16	.	*	F	2.76	1.32
	Gly	710	.	.	.	T	T	.	0.62	.	*	F	3.40	1.32
	Asp	711	.	B	.	.	.	.	1.09	.	*	F	2.31	0.84
	Val	712	.	B	.	.	T	.	1.30	.	*	F	2.17	0.43
35	Pro	713	.	B	.	.	T	.	1.17	*	*	F	1.53	0.75
	Gly	714	.	.	.	T	T	.	0.24	*	*	F	1.59	0.44
	Gly	715	.	.	.	T	T	.	-0.22	.	.	F	0.35	0.49
	Gln	716	.	A	B	.	.	.	-0.22	.	.	F	-0.45	0.26
	Gly	717	.	A	B	.	.	.	0.63	*	.	F	-0.45	0.46
40	Leu	718	.	A	B	.	.	.	0.03	*	.	F	-0.45	0.80
	Leu	719	.	A	B	.	.	.	0.38	*	.	F	-0.45	0.38
	Gln	720	.	A	B	.	.	.	-0.09	*	.	.	-0.30	0.64
	Gln	721	.	A	B	.	.	.	-0.94	*	.	.	-0.60	0.64
	Leu	722	.	A	B	.	.	.	-0.81	.	.	.	-0.60	0.58
45	Asp	723	.	A	B	.	.	.	-0.59	*	.	.	-0.30	0.52
	Leu	724	.	A	B	.	.	.	-0.48	.	.	.	-0.30	0.30
	Val	725	.	A	B	.	.	.	-0.78	.	*	.	-0.60	0.32
	Pro	726	.	A	B	.	.	.	-1.59	.	*	.	-0.60	0.25
	Ala	727	.	A	B	.	.	.	-1.48	.	*	.	-0.60	0.25
	Phe	728	.	A	B	.	.	.	-1.37	*	.	.	-0.60	0.30
	Ser	729	.	A	B	.	.	.	-0.56	*	.	.	-0.60	0.38
	Leu	730	.	A	B	.	.	.	-0.51	*	.	.	-0.30	0.64
	Phe	731	A	A	.	.	.	.	-1.11	*	.	.	-0.30	0.61

5	Arg	732	A	A	.	.	.	.	.	-0.52	*	.	.	-0.30	0.38
	Glu	733	A	A	.	.	.	.	.	0.14	*	.	.	-0.30	0.79
	Leu	734	A	A	.	.	.	.	.	0.41	*	*	.	-0.15	1.25
	Leu	735	A	A	.	.	.	.	.	0.88	*	.	.	0.30	0.87
	Gln	736	.	A	.	.	T	.	.	0.77	*	*	.	0.10	0.49
10	His	737	.	A	.	.	T	.	.	-0.20	*	.	.	-0.20	0.49
	His	738	.	A	.	B	.	.	C	-0.41	.	.	.	-0.40	0.45
	Gly	739	.	.	.	B	.	.	C	0.40	.	.	.	-0.40	0.40
	Leu	740	.	.	.	B	.	.	C	0.32	.	*	.	-0.40	0.51
	Val	741	.	.	.	B	.	.	C	0.32	.	*	.	-0.40	0.26
15	Pro	742	.	A	B	.	.	.	.	-0.23	.	.	.	-0.30	0.46
	Gln	743	.	A	B	.	.	.	.	-0.79	.	.	F	-0.30	0.56
	Ile	744	.	A	B	.	.	.	.	-0.76	.	.	.	-0.30	0.76
	Glu	745	.	A	B	.	.	.	.	-0.53	.	*	.	0.30	0.71
	Ala	746	.	A	B	.	.	.	.	0.08	.	.	.	-0.30	0.41
20	Ala	747	.	A	B	B	.	.	.	-0.02	.	*	.	-0.60	0.93
	Thr	748	.	A	B	B	.	.	.	-0.91	.	*	.	-0.30	0.77
	Ala	749	.	A	B	B	.	.	.	-0.72	.	.	.	-0.60	0.54
	Tyr	750	.	A	B	B	.	.	.	-1.58	.	.	.	-0.60	0.46
	Thr	751	.	.	B	B	.	.	.	-1.20	.	.	.	-0.60	0.24
25	Ile	752	.	.	B	B	.	.	.	-0.92	.	.	.	-0.60	0.36
	Phe	753	.	.	B	B	.	.	.	-0.61	*	.	.	-0.60	0.33
	Val	754	.	.	B	B	.	.	.	0.09	*	.	.	-0.60	0.37
	Pro	755	.	.	B	.	.	T	.	0.03	*	.	F	0.10	1.04
	Thr	756	.	.	.	.	.	T	C	-0.47	*	.	F	0.60	1.60
30	Asn	757	.	.	.	.	.	T	C	0.42	*	.	F	0.60	1.78
	Arg	758	.	.	.	.	.	T	C	0.53	.	.	F	1.50	1.99
	Ser	759	.	A	.	.	.	.	C	1.39	.	.	F	1.10	1.40
	Leu	760	.	A	B	.	.	.	.	1.26	*	*	F	0.90	1.50
	Glu	761	.	A	B	.	.	.	.	1.57	*	*	F	0.75	0.76
35	Ala	762	.	A	.	.	T	.	.	1.27	*	*	F	0.85	0.91
	Gln	763	.	A	.	.	T	.	.	0.86	*	*	F	1.00	1.48
	Gly	764	.	A	.	.	T	.	.	1.12	.	*	F	1.00	1.15
	Asn	765	.	.	.	.	.	T	C	1.12	.	*	F	0.60	1.54
	Ser	766	.	.	.	.	.	T	C	1.12	.	*	F	0.45	0.74
40	Ser	767	.	.	.	.	.	T	C	1.12	.	*	F	1.20	1.24
	His	768	.	.	.	.	.	T	C	1.12	.	*	F	1.31	0.78
	Leu	769	.	.	.	.	.	.	C	1.16	.	.	.	1.52	0.97
	Asp	770	.	.	.	.	T	T	.	0.30	*	.	.	2.03	1.05
	Ala	771	.	.	B	.	.	T	.	0.71	*	*	F	1.89	0.57
45	Asp	772	.	.	B	.	.	T	.	0.98	.	*	F	2.60	1.36
	Thr	773	.	.	B	.	.	T	.	0.98	.	*	F	2.34	1.10
	Val	774	.	.	B	B	.	.	.	0.93	.	.	.	1.23	1.49
	Arg	775	.	.	B	B	.	.	.	0.08	.	*	.	0.82	0.66
	His	776	.	.	B	B	.	.	.	-0.14	*	*	.	-0.34	0.34
50	His	777	.	.	B	B	.	.	.	-0.49	*	*	.	-0.60	0.38
	Val	778	.	.	B	B	.	.	.	-0.18	.	*	.	-0.60	0.19
	Val	779	.	.	B	B	.	.	.	0.09	*	*	.	-0.60	0.24
	Leu	780	.	.	B	B	.	.	.	-0.83	*	*	.	-0.60	0.18

5	Gly	781	.	.	B	B	.	.	.	-1.10	.	.	.	-0.60	0.20
	Glu	782	A	A	.	.	.	.	.	-1.67	.	.	.	-0.30	0.36
	Ala	783	A	A	.	.	.	.	.	-0.81	.	.	.	-0.30	0.43
	Leu	784	A	A	.	.	.	.	.	-0.27	.	.	.	0.30	0.76
	Ser	785	A	A	.	.	.	.	.	-0.27	*	.	.	0.30	0.63
10	Met	786	A	A	.	.	.	.	.	0.19	*	.	.	-0.30	0.52
	Glu	787	A	A	.	.	.	.	.	0.23	*	.	.	0.45	1.23
	Thr	788	A	A	.	.	.	.	.	0.48	*	.	F	1.24	1.83
	Leu	789	A	A	.	.	.	.	.	0.94	*	.	F	1.58	1.83
	Arg	790	.	.	.	.	T	T	.	1.21	*	.	F	2.72	1.05
15	Lys	791	.	.	.	.	T	T	.	1.92	*	.	F	2.61	0.99
	Gly	792	.	.	.	.	T	T	.	1.92	*	.	F	3.40	2.34
	Gly	793	.	.	.	.	.	T	C	1.93	*	*	F	2.86	1.92
	His	794	.	.	.	.	.	T	C	1.93	*	.	F	2.52	1.29
	Arg	795	.	.	B	.	.	T	.	1.01	*	.	F	1.68	1.07
20	Asn	796	.	.	B	.	.	T	.	0.62	.	*	F	0.59	0.90
	Ser	797	.	.	B	.	.	T	.	0.76	.	.	F	0.25	0.65
	Leu	798	.	.	B	.	.	.	.	0.51	.	.	F	0.05	0.51
	Leu	799	.	.	.	.	.	.	C	0.51	.	*	F	-0.05	0.32
	Gly	800	.	.	.	.	.	.	C	0.11	*	*	F	-0.05	0.33
25	Pro	801	.	.	.	.	.	.	C	-0.78	*	.	.	-0.20	0.42
	Ala	802	.	.	B	B	.	.	.	-1.33	.	.	.	-0.60	0.36
	His	803	.	.	B	B	.	.	.	-1.22	.	.	.	-0.60	0.27
	Trp	804	.	.	B	B	.	.	.	-0.66	.	.	.	-0.60	0.15
	Ile	805	.	.	B	B	.	.	.	-0.31	.	.	.	-0.60	0.23
30	Val	806	.	.	B	B	.	.	.	-0.13	.	.	.	-0.60	0.27
	Phe	807	.	.	B	B	.	.	.	0.16	.	.	.	-0.60	0.35
	Tyr	808	.	.	B	.	.	.	.	-0.16	.	.	.	-0.40	0.68
	Asn	809	.	.	.	.	T	.	.	0.13	.	.	.	0.24	0.90
	His	810	.	.	.	.	T	T	.	0.81	.	.	F	0.98	1.81
35	Ser	811	.	.	.	.	.	T	C	1.67	.	*	F	1.32	1.78
	Gly	812	.	.	.	.	.	T	C	1.51	.	*	F	2.16	1.92
	Gln	813	.	.	.	.	.	T	C	1.76	.	*	F	2.40	1.05
	Pro	814	.	.	.	.	.	.	C	1.72	*	*	F	1.96	1.26
	Glu	815	.	.	B	.	.	.	.	0.90	*	*	F	1.52	1.73
40	Val	816	.	.	B	.	.	.	.	0.99	.	*	.	0.38	0.74
	Asn	817	.	.	B	.	.	.	.	0.52	.	*	.	0.14	0.74
	His	818	.	.	B	.	.	.	.	0.52	.	*	.	-0.10	0.35
	Val	819	.	.	B	.	.	.	.	0.39	.	.	.	-0.10	0.82
	Pro	820	.	.	.	.	.	.	C	0.18	.	*	.	0.10	0.51
45	Leu	821	.	.	.	.	.	.	C	0.43	.	.	.	0.10	0.57
	Glu	822	.	.	.	.	.	.	C	-0.38	.	.	F	0.25	0.77
	Gly	823	.	.	B	.	.	.	.	-0.34	.	*	F	0.05	0.41
	Pro	824	.	A	B	.	.	.	.	-0.08	.	*	F	0.45	0.86
	Met	825	.	A	B	.	.	.	.	-0.08	.	.	.	0.30	0.50
	Leu	826	.	A	B	.	.	.	.	0.39	*	*	.	0.01	0.78
	Glu	827	.	A	B	.	.	.	.	0.50	*	*	.	0.32	0.50
	Ala	828	.	.	B	.	.	T	.	0.54	*	*	F	1.78	0.99
	Pro	829	.	.	.	.	.	T	C	-0.06	*	*	F	2.74	1.61

5	Gly	830	.	.	.	T	T	.	-0.34	*	*	F	3.10	0.77
	Arg	831	.	.	B	.	T	.	0.12	*	*	F	1.49	0.53
	Ser	832	.	.	B	B	.	.	-0.69	*	*	F	0.78	0.34
	Leu	833	.	.	B	B	.	.	-0.40	.	*	.	0.32	0.28
	Ile	834	.	.	B	B	.	.	-0.53	.	*	.	0.01	0.19
10	Gly	835	.	.	B	B	.	.	-1.04	*	*	.	-0.60	0.14
	Leu	836	.	.	B	B	.	.	-1.97	*	*	.	-0.60	0.13
	Ser	837	.	.	B	B	.	.	-1.98	.	.	.	-0.60	0.15
	Gly	838	.	.	B	B	.	.	-2.02	.	.	.	-0.60	0.22
	Val	839	.	.	B	B	.	.	-1.48	.	*	.	-0.60	0.20
15	Leu	840	.	.	B	B	.	.	-1.43	*	.	.	-0.60	0.15
	Thr	841	.	.	B	B	.	.	-0.92	.	*	.	-0.60	0.20
	Val	842	.	.	B	B	.	.	-0.51	.	.	F	-0.45	0.36
	Gly	843	.	.	B	.	.	.	-0.83	.	.	F	0.05	0.85
	Ser	844	.	.	B	.	T	.	-0.79	.	.	F	0.85	0.32
20	Ser	845	.	.	B	.	T	.	-0.01	*	.	F	0.25	0.35
	Arg	846	.	.	B	.	T	.	0.00	.	.	F	0.85	0.49
	Cys	847	.	.	B	.	T	.	0.82	.	.	.	0.70	0.49
	Leu	848	.	A	B	.	.	.	0.58	*	.	.	-0.30	0.49
	His	849	.	A	.	.	.	C	0.88	*	.	.	-0.10	0.25
25	Ser	850	.	A	.	.	.	C	0.59	*	.	.	-0.10	0.82
	His	851	.	A	.	.	.	C	-0.33	*	.	.	0.05	1.01
	Ala	852	A	A	.	.	.	.	0.44	*	.	.	-0.30	0.61
	Glu	853	A	A	.	.	.	.	1.26	*	*	.	0.30	0.89
	Ala	854	A	A	.	.	.	.	1.33	*	*	.	0.75	1.13
30	Leu	855	A	A	.	.	.	.	0.97	.	.	.	1.03	2.24
	Arg	856	A	A	.	.	.	.	0.14	.	.	F	1.31	0.69
	Glu	857	.	A	.	.	T	.	0.73	.	.	F	1.99	0.51
	Lys	858	.	A	.	.	T	.	0.07	.	.	F	2.27	0.99
	Cys	859	.	.	.	.	T	T	0.34	*	*	.	2.80	0.27
35	Val	860	.	.	.	.	T	T	1.27	*	*	.	2.22	0.23
	Asn	861	.	.	.	.	T	T	1.27	*	*	.	2.21	0.22
	Cys	862	.	.	B	.	.	T	0.57	*	*	.	1.80	0.81
	Thr	863	.	.	.	.	T	.	0.63	*	*	.	1.99	0.95
	Arg	864	.	.	.	.	T	.	0.63	*	*	.	2.43	1.15
40	Arg	865	.	.	.	.	T	.	1.18	*	*	.	2.70	1.15
	Phe	866	.	.	.	.	T	.	1.18	*	*	.	2.43	1.15
	Arg	867	.	.	.	.	T	.	1.50	*	*	.	2.16	1.02
	Cys	868	.	.	.	.	T	T	1.11	.	*	.	1.64	0.52
	Thr	869	.	.	.	.	T	T	1.00	.	*	F	0.62	0.52
45	Gln	870	.	.	.	.	T	T	0.08	.	*	F	0.65	0.46
	Gly	871	.	.	.	.	T	T	0.78	.	*	F	0.35	0.70
	Phe	872	.	.	B	.	.	.	0.67	.	*	.	-0.40	0.84
	Gln	873	.	.	B	.	.	.	1.02	.	.	.	-0.10	0.81
	Leu	874	.	.	B	.	.	.	1.12	.	*	.	0.39	1.18
	Gln	875	.	.	B	.	.	.	1.23	*	*	F	0.88	2.11
	Asp	876	.	.	.	.	T	.	1.62	*	*	F	2.52	2.39
	Thr	877	.	.	.	.	.	T	2.02	*	*	F	2.86	5.80
	Pro	878	.	.	.	.	T	T	1.36	*	*	F	3.40	4.48

5	Arg	879	.	.	.	.	T	T	.	1.31	*	.	F	3.06	1.44
	Lys	880	.	.	.	.	T	T	.	1.07	.	.	F	2.27	0.74
	Ser	881	.	.	B	B	.	.	.	1.18	.	.	.	0.98	0.75
	Cys	882	.	.	B	B	.	.	.	1.19	.	.	.	0.94	0.75
	Val	883	.	.	B	B	.	.	.	1.06	.	*	.	0.30	0.50
10	Tyr	884	.	.	B	.	.	T	.	0.24	.	*	.	0.10	0.37
	Arg	885	.	.	B	.	.	T	.	-0.10	*	*	F	-0.05	0.60
	Ser	886	.	.	B	.	.	T	.	-0.50	*	*	F	0.40	1.08
	Gly	887	.	.	.	.	T	T	.	-0.13	*	.	F	0.35	0.60
	Phe	888	.	.	.	.	T	.	.	0.83	*	.	.	0.30	0.41
15	Ser	889	.	.	B	.	.	.	.	0.73	*	*	.	0.00	0.60
	Phe	890	.	.	.	.	T	.	.	-0.04	*	*	.	0.50	0.60
	Ser	891	.	.	.	.	T	T	.	-0.04	*	.	.	0.80	0.37
	Arg	892	.	.	.	.	T	T	.	0.06	*	.	F	1.65	0.37
	Gly	893	.	.	.	.	T	T	.	0.44	*	.	.	1.00	0.67
20	Cys	894	.	.	.	.	T	T	.	0.08	*	.	.	0.90	0.72
	Ser	895	.	.	.	B	T	.	.	0.19	*	.	.	0.40	0.20
	Tyr	896	.	.	.	B	T	.	.	0.53	.	.	.	0.00	0.20
	Thr	897	.	.	.	B	T	.	.	0.47	.	*	.	0.20	0.75
	Cys	898	.	.	B	B	.	.	.	-0.08	*	.	.	0.45	1.12
25	Ala	899	.	.	.	B	T	.	.	0.59	.	*	.	0.10	0.50
	Lys	900	.	.	B	.	.	.	.	0.03	.	*	.	0.50	0.60
	Lys	901	.	.	B	.	.	.	.	0.07	.	.	F	0.65	0.83
	Ile	902	.	.	B	.	.	.	.	0.38	.	.	F	0.80	1.28
	Gln	903	.	.	B	.	.	.	.	0.38	.	.	.	0.95	1.07
30	Val	904	.	.	B	.	.	T	.	0.30	.	.	.	0.70	0.29
	Pro	905	.	.	B	.	.	T	.	0.04	.	.	.	0.10	0.22
	Asp	906	.	.	.	.	T	T	.	-0.34	.	*	.	0.50	0.20
	Cys	907	.	.	B	.	.	T	.	-0.16	*	.	.	0.10	0.26
	Cys	908	.	.	B	.	.	T	.	-0.86	*	.	.	0.10	0.15
35	Pro	909	.	.	.	.	T	T	.	-0.34	*	.	.	0.20	0.08
	Gly	910	.	.	.	.	T	T	.	-0.44	*	.	.	0.20	0.14
	Phe	911	.	.	.	.	T	T	.	-1.26	*	.	.	0.20	0.38
	Phe	912	.	.	.	.	T	.	.	-1.26	.	.	.	0.00	0.20
	Gly	913	.	.	.	.	T	.	.	-0.59	*	.	.	0.00	0.11
40	Thr	914	.	.	B	.	.	.	.	-0.59	*	.	.	-0.40	0.22
	Leu	915	.	.	.	.	T	.	.	-0.91	.	.	.	0.30	0.39
	Cys	916	.	.	B	.	.	.	.	-0.42	*	.	.	0.15	0.21
	Glu	917	.	.	B	.	.	.	.	-0.07	.	.	F	0.55	0.22
	Pro	918	.	.	.	.	T	.	.	-0.07	.	.	F	1.20	0.27
45	Cys	919	.	.	.	.	T	T	.	-0.57	.	.	F	2.25	0.50
	Pro	920	.	.	.	.	T	T	.	-0.10	.	.	F	2.50	0.24
	Gly	921	.	.	.	.	T	T	.	0.22	.	.	F	1.35	0.15
	Gly	922	.	.	.	.	T	T	.	-0.63	.	.	F	1.10	0.28
	Leu	923	.	.	.	B	T	.	.	-1.09	.	.	F	0.45	0.13
	Gly	924	.	.	B	B	.	.	.	-0.72	.	.	F	-0.20	0.07
	Gly	925	.	.	B	B	.	.	.	-0.86	.	.	.	-0.60	0.10
	Val	926	.	.	B	B	.	.	.	-0.54	.	.	.	-0.60	0.12
	Cys	927	.	.	B	.	.	T	.	-0.54	.	.	.	0.10	0.16

5	Ser	928	.	.	B	.	.	T	.	0.27	.	.	.	0.10	0.16
	Gly	929	.	.	.	.	T	T	.	-0.06	.	*	F	0.91	0.38
	His	930	.	.	.	.	T	T	.	0.29	.	.	F	1.17	0.38
	Gly	931	.	.	.	.	T	.	.	1.14	*	*	F	1.23	0.49
	Gln	932	.	.	.	.	T	.	.	1.92	*	*	F	2.09	0.83
10	Cys	933	.	.	B	.	.	T	.	1.52	*	*	F	2.60	1.19
	Gln	934	.	.	B	.	.	T	.	1.06	*	*	F	2.04	1.04
	Asp	935	.	.	B	.	.	T	.	0.74	*	*	F	1.88	0.50
	Arg	936	.	.	B	.	.	T	.	0.79	*	*	.	1.72	0.92
	Phe	937	.	.	.	.	T	.	.	0.44	*	*	.	1.91	0.71
15	Leu	938	.	.	.	.	T	.	.	1.11	*	*	F	2.05	0.42
	Gly	939	.	.	.	.	T	T	.	0.44	*	*	F	2.50	0.37
	Ser	940	.	.	.	.	T	T	.	0.41	*	*	F	1.65	0.23
	Gly	941	.	.	.	.	T	T	.	-0.37	*	*	F	1.40	0.38
	Glu	942	.	.	.	.	T	T	.	0.30	.	.	F	1.75	0.21
20	Cys	943	.	.	.	.	T	.	.	1.11	.	.	.	1.15	0.21
	His	944	.	.	.	.	T	.	.	1.11	.	*	.	0.90	0.37
	Cys	945	.	.	B	.	.	T	.	0.71	.	.	.	0.70	0.21
	His	946	.	.	.	.	T	T	.	1.02	.	*	.	0.50	0.34
	Glu	947	.	.	.	.	T	T	.	0.68	.	.	.	0.50	0.34
25	Gly	948	.	.	.	.	T	T	.	1.03	.	.	.	0.50	0.62
	Phe	949	.	.	.	.	T	.	.	0.48	.	.	.	0.30	0.66
	His	950	.	.	.	.	T	.	.	0.48	.	.	.	0.30	0.39
	Gly	951	.	.	.	.	T	.	.	0.51	*	.	.	0.00	0.21
	Thr	952	.	A	.	.	T	.	.	-0.34	*	.	.	0.10	0.42
30	Ala	953	.	A	.	.	T	.	C	-0.67	*	.	.	0.10	0.23
	Cys	954	.	A	B	.	.	.	.	0.03	*	.	.	-0.30	0.12
	Glu	955	.	A	B	.	.	.	.	-0.74	.	.	.	0.30	0.15
	Val	956	.	A	B	.	.	.	.	-0.74	*	.	.	0.30	0.12
	Cys	957	.	A	B	.	.	.	.	-0.32	*	.	.	0.30	0.22
35	Glu	958	.	A	B	.	.	.	.	0.02	*	.	.	0.60	0.25
	Leu	959	.	A	B	.	.	.	.	0.34	*	.	.	-0.30	0.53
	Gly	960	.	A	.	.	T	.	.	0.13	*	.	.	0.83	0.98
	Arg	961	.	.	.	.	T	.	.	0.99	*	.	F	1.31	0.88
	Tyr	962	.	.	.	.	T	.	.	0.99	*	.	F	0.99	1.71
40	Gly	963	.	.	.	.	.	T	C	0.68	*	*	F	0.97	0.93
	Pro	964	.	.	.	.	T	T	.	1.14	*	.	F	1.30	0.68
	Asn	965	.	.	.	.	T	T	.	0.63	*	*	F	0.87	0.43
	Cys	966	.	.	.	.	T	T	.	-0.14	*	*	F	1.04	0.32
	Thr	967	.	.	B	B	.	.	.	0.10	.	.	F	-0.19	0.11
45	Gly	968	.	.	B	B	.	.	.	-0.22	.	.	.	-0.17	0.12
	Val	969	.	.	B	B	.	.	.	-0.60	.	.	.	-0.30	0.12
	Cys	970	.	.	B	B	.	.	.	-0.63	.	.	.	-0.30	0.08
	Asp	971	.	.	B	B	.	.	.	-0.31	*	.	.	-0.30	0.11
	Cys	972	.	.	B	.	.	T	.	-0.81	*	.	.	0.10	0.15
	Ala	973	.	.	.	.	T	T	.	-1.13	*	.	.	0.50	0.23
	His	974	.	.	.	.	T	T	.	-0.28	*	.	.	0.50	0.07
	Gly	975	.	.	.	.	T	T	.	0.39	*	.	.	0.20	0.24
	Leu	976	.	.	B	.	.	.	.	0.04	*	.	.	-0.10	0.41

5	Cys	977	.	B	.	.	T	.	-0.10	*	.	.	0.10	0.30
	Gln	978	.	B	.	.	T	.	0.49	*	.	.	0.37	0.25
	Glu	979	.	B	.	.	T	.	0.18	.	*	F	0.79	0.52
	Gly	980	.	B	.	.	T	.	0.52	.	*	F	1.66	0.96
	Leu	981	.	.	.	.	.	.	0.99	.	*	F	2.43	0.93
10	Gln	982	.	.	.	T	.	.	1.36	.	*	F	2.70	0.53
	Gly	983	.	.	.	T	T	.	0.69	*	*	F	2.33	0.72
	Asp	984	.	.	.	T	T	.	-0.17	.	.	F	2.06	0.47
	Gly	985	.	.	.	T	T	.	-0.49	.	*	F	1.79	0.20
	Ser	986	.	.	.	T	T	.	0.32	*	*	F	0.92	0.11
15	Cys	987	.	B	B	.	.	.	-0.53	.	*	.	-0.30	0.10
	Val	988	.	B	B	.	.	.	-0.53	.	*	.	-0.60	0.08
	Cys	989	.	B	B	.	.	.	-0.82	*	*	.	-0.60	0.06
	Asn	990	.	B	.	.	T	.	-0.48	*	*	.	-0.20	0.11
	Val	991	.	B	.	.	T	.	-0.52	*	.	.	-0.20	0.26
20	Gly	992	.	.	.	T	T	.	-0.67	*	.	.	0.20	0.49
	Trp	993	.	.	.	T	T	.	0.30	*	.	.	0.20	0.25
	Gln	994	.	B	.	.	.	.	0.30	*	*	.	-0.40	0.66
	Gly	995	.	B	.	.	.	.	0.30	*	*	.	-0.40	0.36
	Leu	996	A	B	.	.	.	.	1.16	*	*	.	-0.30	0.57
25	Arg	997	A	B	.	.	.	.	1.54	*	*	.	0.60	0.57
	Cys	998	A	.	.	T	.	.	0.94	*	*	F	1.30	1.15
	Asp	999	A	.	.	T	.	.	0.63	*	*	F	1.15	0.98
	Gln	1000	A	.	B	T	.	.	0.68	*	*	F	1.15	0.72
	Lys	1001	A	.	B	T	.	.	1.28	*	*	F	1.00	1.80
30	Ile	1002	A	.	B	T	.	.	1.17	*	*	F	1.30	1.66
	Thr	1003	.	B	B	.	.	.	1.17	.	.	F	0.60	1.66
	Ser	1004	.	B	B	.	.	.	0.96	.	*	F	0.45	0.45
	Pro	1005	.	.	.	T	.	.	1.07	.	.	F	0.45	0.98
	Gln	1006	.	.	.	T	.	.	1.07	.	.	F	1.54	1.34
35	Cys	1007	.	B	.	.	T	.	1.29	.	.	F	1.98	1.99
	Pro	1008	.	.	.	T	T	.	1.60	*	.	F	2.57	0.69
	Arg	1009	.	.	.	T	T	.	1.69	*	.	F	2.91	0.67
	Lys	1010	.	.	.	T	T	.	1.90	*	.	F	3.40	1.92
	Cys	1011	.	.	.	T	.	.	1.31	*	*	F	2.86	2.00
40	Asp	1012	.	.	.	T	T	.	1.98	*	*	F	2.72	1.03
	Pro	1013	.	.	.	T	T	.	1.52	*	.	F	2.23	0.83
	Asn	1014	.	.	.	T	T	.	0.56	*	.	F	1.59	0.83
	Ala	1015	.	B	.	.	T	.	0.51	*	*	.	0.70	0.37
	Asn	1016	.	B	.	.	.	.	1.18	*	*	.	-0.10	0.41
45	Cys	1017	.	B	.	.	.	.	0.88	*	.	.	0.50	0.43
	Val	1018	.	B	.	.	T	.	0.50	.	.	.	0.91	0.57
	Gln	1019	.	B	.	.	T	.	0.16	.	.	.	1.12	0.36
	Asp	1020	.	B	.	.	T	.	0.16	.	.	F	1.48	0.66
	Ser	1021	.	.	.	T	T	.	-0.14	.	.	F	2.09	0.90
	Ala	1022	.	.	.	T	.	.	0.21	.	.	F	2.10	0.69
	Gly	1023	.	.	.	T	.	.	0.40	.	.	F	1.89	0.60
	Ala	1024	.	.	.	T	.	.	-0.19	.	.	F	1.08	0.24
	Ser	1025	.	B	.	.	T	.	-0.86	.	.	F	0.67	0.24



5	Thr	1026.	.	B	.	.	T	.	-1.14	.	.	.	0.01	0.13
	Cys	1027.	.	B	.	.	T	.	-1.14	.	.	.	-0.20	0.13
	Ala	1028.	.	B	.	.	T	.	-1.14	.	.	.	-0.20	0.10
	Cys	1029.	A	B	.	.	.	.	-0.80	.	.	.	-0.60	0.07
	Ala	1030.	A	B	.	.	.	.	-0.80	.	.	.	-0.60	0.20
10	Ala	1031.	A	B	.	.	.	.	-0.83	.	.	.	-0.60	0.26
	Gly	1032.	A	.	.	T	.	.	-0.17	.	.	.	-0.20	0.48
	Tyr	1033.	.	.	.	T	.	.	0.08	.	.	.	0.00	0.77
	Ser	1034.	.	.	.	T	T	.	-0.14	.	.	F	0.65	0.75
	Gly	1035.	.	.	.	T	T	.	-0.26	.	.	F	0.35	0.53
15	Asn	1036.	.	.	.	T	T	.	-0.33	.	.	F	0.35	0.29
	Gly	1037.	.	.	.	T	T	.	-0.29	.	.	F	0.35	0.12
	Ile	1038.	.	B	B	.	.	.	-0.04	.	.	.	-0.60	0.16
	Phe	1039.	.	B	B	.	.	.	-0.60	.	*	.	-0.30	0.17
	Cys	1040.	.	B	B	.	.	.	-0.26	.	*	.	-0.60	0.13
20	Ser	1041.	.	B	.	.	.	.	-0.47	.	*	.	0.12	0.31
	Glu	1042.	.	B	.	.	.	.	-0.79	.	*	F	1.09	0.55
	Val	1043.	.	.	.	T	.	.	-0.49	*	*	F	1.71	0.55
	Asp	1044.	.	.	.	.	T	C	0.18	*	*	F	1.93	0.41
	Pro	1045.	.	.	.	T	T	.	0.50	.	*	.	2.20	0.32
25	Cys	1046.	.	.	.	T	T	.	0.77	.	*	.	1.38	0.43
	Ala	1047.	.	B	.	.	T	.	0.42	.	*	.	1.36	0.35
	His	1048.	.	.	.	T	.	.	0.93	.	*	.	0.74	0.23
	Gly	1049.	.	.	.	T	.	.	0.27	.	*	.	0.52	0.42
	His	1050.	.	.	.	T	T	.	0.18	.	.	.	0.50	0.22
30	Gly	1051.	.	.	.	T	T	.	0.63	.	.	F	0.65	0.22
	Gly	1052.	.	.	.	T	T	.	1.19	.	*	F	0.65	0.34
	Cys	1053.	.	.	.	T	T	.	0.63	.	*	F	0.65	0.34
	Ser	1054.	.	.	.	.	.	C	0.98	.	*	F	0.25	0.35
	Pro	1055.	.	.	.	T	.	.	0.34	.	*	F	0.45	0.56
35	His	1056.	.	.	.	T	T	.	0.38	.	.	.	0.50	0.56
	Ala	1057.	.	.	.	T	T	.	0.77	.	.	.	0.50	0.61
	Asn	1058.	.	.	.	T	T	.	0.58	.	.	.	1.10	0.78
	Cys	1059.	.	B	.	.	T	.	0.29	.	.	.	0.10	0.43
	Thr	1060.	.	B	.	.	.	.	0.29	.	.	.	0.21	0.43
40	Lys	1061.	.	B	.	.	.	.	-0.02	.	.	F	0.67	0.41
	Val	1062.	.	B	.	.	.	.	0.57	.	.	F	0.98	0.76
	Ala	1063.	.	B	.	.	T	.	0.68	.	.	F	2.09	0.91
	Pro	1064.	.	.	.	T	T	.	1.03	*	.	F	3.10	0.89
	Gly	1065.	.	.	.	T	T	.	0.68	*	.	F	2.64	1.73
45	Gln	1066.	.	.	.	T	T	.	0.32	.	.	F	2.18	0.92
	Arg	1067.	.	.	.	T	.	.	0.51	.	.	F	1.67	0.86
	Thr	1068.	.	B	.	.	.	.	1.10	.	.	F	0.96	0.47
	Cys	1069.	.	B	.	.	.	.	1.31	.	.	.	0.50	0.47
	Thr	1070.	.	B	.	.	.	.	1.31	.	.	.	0.50	0.40
	Cys	1071.	.	B	.	.	T	.	1.07	.	.	.	0.70	0.27
	Gln	1072.	.	B	.	.	T	.	0.36	.	.	.	0.10	0.80
	Asp	1073.	.	.	.	T	T	.	0.32	.	.	.	0.78	0.55
	Gly	1074.	.	.	.	T	T	.	0.99	.	.	.	1.21	1.01

5	Tyr	1075.	.	.	.	T	.	.	0.96	.	.	.	1.74	0.97
	Met	1076.	.	.	.	T	T	.	1.62	.	*	.	2.22	0.58
	Gly	1077.	.	.	.	T	T	.	0.81	.	.	F	2.80	1.01
	Asp	1078.	.	.	.	T	T	.	0.14	.	.	F	2.37	0.53
	Gly	1079.	.	.	.	.	T	C	0.49	.	.	F	1.89	0.29
10	Glu	1080.	A	B	.	.	.	.	0.73	.	*	F	1.01	0.50
	Leu	1081.	A	B	.	.	.	.	0.44	.	*	.	0.88	0.52
	Cys	1082.	A	B	.	.	.	.	0.79	*	*	.	0.30	0.37
	Gln	1083.	A	B	.	.	.	.	0.49	*	*	.	0.30	0.34
	Glu	1084.	A	.	.	T	.	.	0.17	*	*	F	0.25	0.56
15	Ile	1085.	A	.	.	T	.	.	-0.64	*	*	F	0.25	0.56
	Asn	1086.	.	.	.	T	T	.	-0.72	*	.	.	0.50	0.27
	Ser	1087.	.	.	.	T	T	.	-0.09	*	.	.	0.20	0.11
	Cys	1088.	.	B	.	.	T	.	-0.12	*	.	.	-0.20	0.21
	Leu	1089.	.	B	.	.	T	.	-0.47	.	.	.	-0.20	0.18
20	Ile	1090.	.	B	.	.	.	.	0.08	.	.	.	-0.40	0.13
	His	1091.	.	.	.	T	.	.	-0.59	.	.	.	0.00	0.24
	His	1092.	.	.	.	T	T	.	-0.32	*	.	.	0.20	0.16
	Gly	1093.	.	.	.	T	T	.	-0.54	*	.	.	0.20	0.30
	Gly	1094.	.	.	.	T	T	.	0.23	*	*	.	0.20	0.16
25	Cys	1095.	.	.	.	T	T	.	0.53	*	*	.	0.20	0.16
	His	1096.	A	.	.	T	.	.	0.57	.	*	.	-0.20	0.16
	Ile	1097.	A	B	.	.	.	.	-0.07	.	*	.	-0.30	0.28
	His	1098.	A	B	.	.	.	.	-0.61	.	*	.	-0.30	0.28
	Ala	1099.	A	B	.	.	.	.	-0.48	.	.	.	-0.60	0.14
30	Glu	1100.	A	B	.	.	.	.	-0.12	.	*	.	-0.30	0.32
	Cys	1101.	A	B	.	.	.	.	-0.43	.	*	.	-0.30	0.34
	Ile	1102.	A	.	.	.	.	C	0.24	.	*	.	-0.10	0.33
	Pro	1103.	.	.	.	T	T	.	0.28	*	.	F	0.65	0.29
	Thr	1104.	.	.	.	T	T	.	0.87	*	.	F	0.35	0.95
35	Gly	1105.	.	.	.	.	T	C	0.01	*	.	F	0.60	2.35
	Pro	1106.	.	.	.	T	T	.	0.38	*	.	F	0.80	1.13
	Gln	1107.	.	.	.	T	.	.	0.60	*	.	F	0.60	1.05
	Gln	1108.	.	B	.	.	.	.	0.51	.	.	F	0.05	0.57
	Val	1109.	.	B	.	.	.	.	0.16	*	*	F	0.05	0.49
40	Ser	1110.	.	B	.	.	.	.	0.61	*	*	.	-0.10	0.15
	Cys	1111.	.	B	.	.	T	.	0.82	*	*	.	0.70	0.17
	Ser	1112.	.	B	.	.	T	.	0.48	*	*	.	0.70	0.40
	Cys	1113.	.	B	.	.	T	.	0.23	*	*	.	1.00	0.30
	Arg	1114.	.	.	.	T	T	.	0.79	*	*	F	1.56	0.87
45	Glu	1115.	.	.	.	T	.	.	0.74	.	*	F	1.67	0.87
	Gly	1116.	.	.	.	T	.	.	1.41	.	*	F	2.13	1.60
	Tyr	1117.	.	.	.	T	.	.	1.37	.	*	F	2.74	1.36
	Ser	1118.	.	.	.	T	T	.	1.14	.	*	F	3.10	0.78
	Gly	1119.	.	.	.	T	T	.	1.14	.	*	F	1.89	0.55
	Asp	1120.	.	.	.	T	T	.	0.83	*	.	F	2.18	0.69
	Gly	1121.	.	.	.	T	T	.	0.51	*	.	F	2.17	0.74
	Ile	1122.	.	B	.	.	.	.	0.76	*	.	F	0.96	0.40
	Arg	1123.	.	B	.	.	.	.	0.24	*	.	F	0.95	0.42

5	Thr	1124.	.	B	.	.	.	-0.22	*	.	F	0.65	0.35
	Cys	1125.	.	B	.	.	.	-0.22	*	.	.	-0.10	0.41
	Glu	1126.	.	B	.	.	.	-0.09	*	*	.	0.80	0.35
	Leu	1127.	.	B	.	.	.	0.13	*	*	.	0.84	0.37
	Leu	1128.	.	B	.	.	.	-0.28	*	.	.	1.18	0.37
10	Asp	1129.	.	B	.	.	T	0.08	*	.	F	1.87	0.29
	Pro	1130.	.	.	.	T	T	0.74	*	.	F	2.61	0.70
	Cys	1131.	.	.	.	T	T	0.74	*	.	F	3.40	1.37
	Ser	1132.	.	.	.	T	T	1.21	.	.	F	3.06	1.32
	Lys	1133.	.	.	.	T	.	1.68	.	*	F	2.20	0.84
15	Asn	1134.	.	.	.	T	T	1.01	.	.	F	2.34	1.56
	Asn	1135.	.	.	.	T	T	0.92	.	.	F	1.98	0.62
	Gly	1136.	.	.	.	T	T	1.38	.	.	F	1.77	0.42
	Gly	1137.	.	.	.	T	T	1.43	.	.	F	1.30	0.40
	Cys	1138.	.	.	.	T	.	0.80	.	.	F	0.67	0.39
20	Ser	1139.	.	B	.	.	T	0.49	.	.	F	0.34	0.40
	Pro	1140.	.	B	.	.	T	-0.18	.	*	F	0.21	0.58
	Tyr	1141.	.	B	.	.	T	0.21	.	.	.	-0.07	0.58
	Ala	1142.	.	B	.	.	T	0.26	.	.	.	0.10	0.87
	Thr	1143.	.	B	.	.	.	0.61	.	*	.	0.24	0.75
25	Cys	1144.	.	B	.	.	T	0.57	.	*	F	0.93	0.69
	Lys	1145.	.	B	.	.	T	0.78	.	*	F	1.87	0.68
	Ser	1146.	.	.	.	T	T	0.68	.	*	F	2.91	0.79
	Thr	1147.	.	.	.	T	T	1.27	*	*	F	3.40	1.45
	Gly	1148.	.	.	.	T	T	1.69	*	*	F	3.06	1.26
30	Asp	1149.	.	.	.	T	T	2.04	*	.	F	2.72	1.84
	Gly	1150.	.	.	.	T	T	1.33	*	.	F	2.38	1.84
	Gln	1151.	.	.	.	T	T	1.32	*	.	F	1.89	0.99
	Arg	1152.	.	B	.	.	.	0.97	.	.	F	0.95	0.86
	Thr	1153.	.	B	.	.	.	1.31	.	.	F	0.65	0.47
35	Cys	1154.	.	B	.	.	T	1.00	.	.	F	0.85	0.45
	Thr	1155.	.	B	.	.	T	0.76	.	.	.	0.70	0.33
	Cys	1156.	.	B	.	.	T	0.72	.	.	.	0.10	0.23
	Asp	1157.	.	B	.	.	T	0.30	.	.	F	0.25	0.59
	Thr	1158.	.	B	.	.	.	-0.24	.	.	F	0.05	0.59
40	Ala	1159.	.	B	.	.	.	0.08	*	.	.	-0.10	0.81
	His	1160.	.	B	.	.	.	0.39	*	.	.	-0.10	0.48
	Thr	1161.	.	B	.	.	.	0.71	*	.	.	-0.10	0.56
	Val	1162.	.	B	.	.	.	-0.10	*	.	.	0.50	0.55
	Gly	1163.	.	.	.	T	T	-0.10	*	.	F	0.65	0.33
45	Asp	1164.	.	.	.	T	T	-0.18	.	*	F	0.65	0.33
	Gly	1165.	.	.	.	T	T	-0.03	.	*	F	0.65	0.24
	Leu	1166.	.	B	.	.	T	-0.31	*	*	.	0.70	0.47
	Thr	1167.	A	B	.	.	.	0.66	*	*	.	0.30	0.29
	Cys	1168.	A	B	.	.	.	0.14	*	*	.	0.30	0.57
	Arg	1169.	A	B	.	.	.	-0.20	*	*	.	0.30	0.51
	Ala	1170.	A	B	.	.	.	-0.67	.	*	.	0.30	0.35
	Arg	1171.	A	B	.	.	.	0.14	*	*	.	0.30	0.54
	Val	1172.	A	B	.	.	.	-0.36	*	*	.	0.60	0.48

5	Gly	1173.	A	B	.	.	.	-0.50	*	*	.	0.30	0.39
	Leu	1174.	A	B	.	.	.	-0.50	*	*	.	-0.30	0.16
	Glu	1175.	A	B	.	.	.	0.09	*	*	.	-0.30	0.43
	Leu	1176.	A	B	.	.	.	0.02	*	*	.	0.60	0.73
	Leu	1177.	A	B	.	.	.	0.84	.	.	.	0.75	1.77
10	Arg	1178 A	A	.	.	.	.	0.60	.	.	F	0.90	1.39
	Asp	1179 A	A	.	.	.	.	1.11	*	.	F	0.90	1.70
	Lys	1180 A	A	.	.	.	.	0.41	*	.	F	0.90	2.76
	His	1181.	A	.	.	.	C	0.52	.	.	.	0.95	1.22
	Ala	1182.	A	.	.	.	C	1.03	.	*	.	0.50	0.63
15	Ser	1183.	A	B	.	.	.	0.11	.	*	.	-0.30	0.42
	Phe	1184.	A	B	.	.	.	0.22	.	*	.	-0.60	0.26
	Phe	1185.	A	B	.	.	.	-0.63	*	*	.	-0.60	0.50
	Ser	1186.	A	B	.	.	.	-1.41	*	*	.	-0.60	0.31
	Leu	1187.	A	B	.	.	.	-0.82	*	.	.	-0.60	0.29
20	Arg	1188.	A	B	.	.	.	-0.77	.	*	.	-0.30	0.58
	Leu	1189 A	A	.	.	.	.	-0.02	.	*	.	-0.30	0.68
	Leu	1190 A	A	.	.	.	.	0.68	.	*	.	0.45	1.66
	Glu	1191 A	A	.	.	.	.	0.17	.	*	.	0.75	1.47
	Tyr	1192.	A	B	.	.	.	1.02	*	*	.	0.79	1.47
25	Lys	1193.	A	B	.	.	.	0.57	.	*	F	1.58	3.55
	Glu	1194.	A	B	.	.	.	1.38	.	*	F	1.92	2.03
	Leu	1195.	.	.	.	T	T	1.84	.	*	F	3.06	2.16
	Lys	1196.	.	.	.	T	T	1.63	.	*	F	3.40	1.07
	Gly	1197.	.	.	.	T	T	1.18	.	*	F	2.91	0.96
30	Asp	1198.	.	.	.	T	.	0.82	.	*	F	2.42	1.00
	Gly	1199.	.	.	.	.	T	-0.07	.	*	F	1.73	0.72
	Pro	1200.	.	.	.	.	T	0.04	.	*	F	0.79	0.51
	Phe	1201.	.	B	.	.	T	-0.86	.	*	.	-0.20	0.27
	Thr	1202.	.	B	.	.	T	-0.72	.	*	.	-0.20	0.20
35	Ile	1203.	.	B	B	.	.	-0.76	.	*	.	-0.60	0.20
	Phe	1204.	.	B	B	.	.	-1.00	.	.	.	-0.60	0.31
	Val	1205.	.	B	B	.	.	-0.79	.	*	.	-0.60	0.22
	Pro	1206.	.	B	B	.	.	-0.90	.	.	.	-0.60	0.52
	His	1207.	A	.	.	.	C	-1.19	.	.	.	-0.40	0.50
40	Ala	1208.	A	.	.	.	C	-0.60	*	.	.	-0.10	0.66
	Asp	1209.	A	.	.	.	C	0.10	*	*	.	-0.10	0.58
	Leu	1210.	A	.	.	.	C	0.14	.	*	.	-0.10	0.68
	Met	1211.	.	B	.	.	T	0.06	*	*	.	0.40	0.56
	Ser	1212.	.	B	.	.	T	0.09	*	*	.	0.70	0.45
45	Asn	1213.	.	.	.	.	T	0.68	*	*	F	1.05	0.94
	Leu	1214.	.	.	.	.	T	0.68	*	*	F	2.40	1.58
	Ser	1215.	.	.	.	.	T	0.68	.	.	F	3.00	2.04
	Gln	1216.	.	.	.	.	T	0.69	*	.	F	2.40	1.05
	Asp	1217 A	.	.	.	.	T	1.10	*	*	F	1.90	1.28
	Glu	1218 A	.	.	.	.	T	0.21	*	*	F	1.90	1.87
	Leu	1219.	A	B	.	.	.	1.13	.	*	.	0.90	0.76
	Ala	1220.	A	B	.	.	.	0.84	.	*	.	0.60	0.89
	Arg	1221.	A	B	.	.	.	0.81	.	*	.	0.60	0.52

5	Ile	1222.	A	B	.	.	.	0.92	.	*	.	0.30	0.86
	Arg	1223.	A	B	.	.	.	0.92	.	*	.	0.75	1.66
	Ala	1224.	A	B	.	.	.	0.92	.	*	.	0.75	1.47
	His	1225.	A	B	.	.	.	0.66	.	*	.	0.45	1.73
	Arg	1226.	.	B	B	.	.	-0.16	*	*	.	0.30	0.65
10	Gln	1227.	.	B	B	.	.	0.84	*	*	.	-0.60	0.56
	Leu	1228.	.	B	B	.	.	0.49	*	*	.	-0.30	0.81
	Val	1229.	.	B	B	.	.	1.04	.	*	.	-0.30	0.65
	Phe	1230.	.	B	B	.	.	0.22	.	*	.	-0.60	0.51
	Arg	1231.	.	B	B	.	.	-0.74	*	*	.	-0.60	0.46
15	Tyr	1232.	.	B	B	.	.	-1.09	.	*	.	-0.60	0.46
	His	1233.	.	B	B	.	.	-0.94	*	*	.	-0.60	0.52
	Val	1234.	.	B	B	.	.	0.02	*	*	.	-0.60	0.14
	Val	1235.	.	B	B	.	.	0.83	*	*	.	-0.60	0.18
	Gly	1236.	.	B	B	.	.	-0.09	*	*	.	0.30	0.26
20	Cys	1237.	A	B	B	.	.	0.27	*	*	.	0.30	0.29
	Arg	1238.	A	B	B	.	.	0.00	*	*	.	0.60	0.75
	Arg	1239.	A	B	B	.	.	0.86	.	*	F	0.90	1.02
	Leu	1240.	A	B	B	.	.	1.71	.	.	F	0.90	3.30
	Arg	1241.	A	B	B	.	.	1.24	.	*	F	0.90	2.81
25	Ser	1242.	A	.	.	.	C	1.10	.	*	F	1.10	1.18
	Glu	1243.	A	B	.	.	.	0.99	.	*	F	0.90	1.18
	Asp	1244.	A	B	.	.	.	0.88	.	*	F	0.90	1.05
	Leu	1245.	A	B	.	.	.	1.34	*	*	F	0.90	1.35
	Leu	1246.	A	B	.	.	.	0.99	*	.	F	0.75	0.77
30	Glu	1247.	.	B	.	.	T	0.70	*	.	F	0.85	0.73
	Gln	1248.	.	B	.	.	T	0.39	*	.	F	-0.05	0.89
	Gly	1249.	.	B	.	.	T	-0.20	*	.	F	0.40	1.55
	Tyr	1250.	.	B	.	.	T	-0.20	*	.	.	0.10	0.91
	Ala	1251.	A	B	.	.	.	0.31	*	.	.	-0.60	0.43
35	Thr	1252.	A	B	.	.	.	-0.03	.	.	.	-0.60	0.58
	Ala	1253.	A	B	.	.	.	-0.07	.	.	.	-0.60	0.37
	Leu	1254.	A	B	.	.	.	0.07	.	.	.	-0.60	0.50
	Ser	1255.	A	B	.	.	.	-0.50	*	.	.	-0.60	0.53
	Gly	1256.	.	.	.	.	C	0.20	*	*	.	-0.20	0.44
40	His	1257.	.	.	.	.	T C	-0.19	.	*	.	0.45	1.03
	Pro	1258.	.	.	.	.	T C	0.10	*	*	.	0.30	0.67
	Leu	1259.	.	.	.	.	T C	0.91	*	*	.	0.30	0.90
	Arg	1260.	.	B	.	.	T	1.32	*	*	.	1.19	1.15
	Phe	1261.	.	B	.	.	.	1.67	*	*	.	1.63	1.46
45	Ser	1262.	.	B	.	.	.	1.36	*	*	F	2.12	3.06
	Glu	1263.	.	.	.	.	C	1.27	*	*	F	2.66	1.55
	Arg	1264.	.	.	.	T	T	1.19	*	*	F	3.40	2.39
	Glu	1265.	.	.	.	T	T	0.83	*	*	F	3.06	1.25
	Gly	1266.	.	.	.	T	T	0.72	.	*	F	2.72	1.13
	Ser	1267.	.	.	.	T	T	1.02	*	.	F	1.93	0.48
	Ile	1268.	.	B	.	.	.	1.02	*	.	.	0.24	0.44
	Tyr	1269.	.	B	.	.	.	0.21	*	.	.	-0.10	0.75
	Leu	1270.	A	B	.	.	.	-0.38	*	*	.	-0.60	0.48

5	Asn	1271.	A	B	.	.	.	0.08	*	*	.	-0.60	0.70
	Asp	1272.	A	B	.	.	.	-0.48	*	*	.	-0.30	0.87
	Phe	1273.	A	B	B	.	.	-0.44	*	*	.	-0.30	0.78
	Ala	1274.	A	B	B	.	.	-0.50	*	.	.	0.30	0.36
	Arg	1275.	A	B	B	.	.	0.01	*	.	.	0.30	0.29
10	Val	1276.	.	B	B	.	.	0.01	*	.	.	0.00	0.45
	Val	1277.	.	B	B	.	.	-0.02	*	.	.	0.90	0.74
	Ser	1278.	.	.	.	.	T	0.68	*	.	F	1.95	0.52
	Ser	1279.	.	.	.	.	T	0.68	*	.	F	2.40	1.20
	Asp	1280.	.	.	.	.	T	-0.29	*	.	F	3.00	1.64
15	His	1281.	.	.	.	.	T	0.57	*	.	F	2.55	0.91
	Glu	1282.	.	.	.	.	C	1.08	*	.	.	2.05	1.09
	Ala	1283.	.	B	.	.	T	0.49	*	.	.	1.60	0.64
	Val	1284.	.	B	.	.	T	-0.02	*	.	.	0.40	0.33
	Asn	1285.	.	B	.	.	T	-0.06	*	.	.	0.10	0.16
20	Gly	1286.	.	B	.	.	T	-0.72	*	.	.	-0.20	0.21
	Ile	1287.	.	B	B	.	.	-1.61	*	.	.	-0.60	0.25
	Leu	1288.	.	B	B	.	.	-1.02	*	.	.	-0.60	0.11
	His	1289.	.	B	B	.	.	-0.06	*	*	.	-0.60	0.18
	Phe	1290.	.	B	B	.	.	-0.91	*	.	.	-0.30	0.51
25	Ile	1291.	.	B	B	.	.	-1.38	*	*	.	-0.30	0.46
	Asp	1292.	.	B	B	.	.	-1.30	*	.	.	-0.30	0.28
	Arg	1293.	.	B	B	.	.	-0.70	*	*	.	-0.60	0.27
	Val	1294.	.	B	B	.	.	-0.88	*	*	.	-0.30	0.59
	Leu	1295.	.	.	B	.	.	-0.18	*	*	.	0.50	0.54
30	Leu	1296.	.	.	B	.	.	0.12	*	.	.	0.50	0.48
	Pro	1297.	.	.	.	.	T	-0.69	.	*	F	0.45	0.65
	Pro	1298.	.	.	.	.	T	-0.83	.	*	F	0.15	0.65
	Glu	1299.	.	.	.	T	T	-0.27	.	.	F	0.80	1.08
	Ala	1300.	.	B	.	.	T	0.54	.	.	.	-0.20	0.73
35	Leu	1301.	.	B	.	.	.	1.14	.	*	.	0.24	0.82
	His	1302.	.	B	.	.	.	1.36	.	.	.	0.58	0.73
	Trp	1303.	.	B	.	.	.	1.57	.	.	.	1.07	1.21
	Glu	1304.	.	.	.	.	T	0.98	.	.	.	2.41	2.45
	Pro	1305.	.	.	.	T	T	1.36	.	.	F	3.40	1.82
40	Asp	1306.	.	.	.	T	T	1.28	.	*	F	3.06	2.67
	Asp	1307.	.	.	.	T	T	1.10	*	.	F	2.98	1.08
	Ala	1308.	.	.	.	.	.	1.50	*	.	F	2.50	1.08
	Pro	1309.	.	.	.	.	.	1.61	.	.	F	2.42	1.27
	Ile	1310.	.	.	.	.	.	1.82	*	.	F	2.34	1.49
45	Pro	1311.	.	B	.	.	T	0.97	*	.	F	2.60	2.37
	Arg	1312.	.	B	.	.	T	0.66	.	.	F	2.04	1.14
	Arg	1313.	.	B	.	.	T	0.66	*	.	F	1.78	2.34
	Asn	1314.	.	B	.	.	T	0.28	*	.	F	1.82	1.53
	Val	1315.	A	B	B	.	.	0.58	*	.	.	0.56	0.79
45	Thr	1316.	A	B	B	.	.	0.79	*	*	.	-0.30	0.41
	Ala	1317.	A	B	B	.	.	0.33	*	.	.	-0.60	0.44
	Ala	1318.	A	B	.	.	.	-0.48	*	.	.	-0.60	0.58
	Ala	1319.	A	B	.	.	.	-0.82	*	*	.	-0.60	0.35

	Gln	1320.	A	B	.	.	.	.	-0.21	.	.	.	-0.60	0.34
	Gly	1321.	.	B	.	.	T	.	0.14	.	*	.	-0.20	0.53
	Phe	1322.	.	B	.	.	T	.	-0.16	.	.	.	0.25	1.05
	Gly	1323.	.	B	.	.	T	.	-0.27	*	.	.	-0.20	0.43
5	Tyr	1324.	.	B	.	.	T	.	0.02	*	.	.	-0.20	0.37
	Lys	1325.	.	B	B	.	.	.	-0.32	*	.	.	-0.60	0.58
	Ile	1326.	.	B	B	.	.	.	-0.79	*	.	.	-0.60	0.58
	Phe	1327.	.	B	B	.	.	.	-0.90	*	*	.	-0.60	0.30
	Ser	1328.	.	B	B	.	.	.	-0.51	*	*	.	-0.60	0.13
10	Gly	1329.	A	B	.	.	.	.	-1.12	*	*	.	-0.60	0.36
	Leu	1330.	A	B	.	.	.	.	-1.76	*	*	.	-0.60	0.31
	Leu	1331.	A	B	.	.	.	.	-1.21	*	.	.	-0.30	0.23
	Lys	1332.	A	B	.	.	.	.	-1.32	*	*	.	-0.30	0.23
	Val	1333.	A	B	.	.	.	.	-1.83	*	*	.	-0.60	0.23
15	Ala	1334.	A	B	.	.	.	.	-1.70	.	*	.	-0.60	0.23
	Gly	1335.	A	B	.	.	.	.	-1.70	.	.	.	-0.30	0.18
	Leu	1336.	A	B	.	.	.	.	-1.70	.	*	.	-0.60	0.20
	Leu	1337.	A	B	.	.	.	.	-1.63	*	*	.	-0.60	0.16
	Pro	1338.	A	B	.	.	.	.	-0.78	*	.	.	-0.60	0.32
20	Leu	1339.	A	B	.	.	.	.	-0.78	*	.	.	-0.30	0.67
	Leu	1340.	A	B	.	.	.	.	-0.73	*	.	.	0.56	0.83
	Arg	1341.	A	B	.	.	.	.	0.04	*	.	.	0.82	0.72
	Glu	1342.	A	B	.	.	.	.	0.97	*	.	F	1.38	1.18
	Ala	1343.	A	.	.	T	.	.	0.97	*	.	F	2.34	2.81
25	Ser	1344.	.	.	.	.	.	C	1.08	*	.	F	2.60	2.21
	His	1345.	.	.	.	.	.	C	1.58	*	.	.	1.89	1.11
	Arg	1346.	.	.	.	.	.	C	0.87	*	.	.	1.03	1.58
	Pro	1347.	.	.	.	T	.	.	0.06	*	.	.	0.97	1.17
	Phe	1348.	.	.	.	T	.	.	0.36	*	.	.	0.26	0.71
30	Thr	1349.	.	B	.	.	.	.	0.44	*	.	.	-0.40	0.38
	Met	1350.	.	B	.	.	.	.	0.17	*	.	.	-0.40	0.38
	Leu	1351.	.	B	.	.	.	.	0.06	*	.	.	-0.40	0.63
	Trp	1352.	.	B	.	.	T	.	-0.32	.	.	.	-0.20	0.73
	Pro	1353.	.	.	.	.	T	C	-0.21	.	.	F	0.15	0.75
35	Thr	1354.	.	.	.	.	T	C	-0.60	*	*	F	0.15	0.92
	Asp	1355.	.	.	.	.	T	C	0.11	*	*	F	0.15	0.75
	Ala	1356.	A	B	.	.	.	.	0.33	*	*	.	0.30	0.96
	Ala	1357.	A	B	.	.	.	.	-0.19	*	*	.	0.30	0.67
	Phe	1358.	A	B	.	.	.	.	-0.19	*	*	.	0.30	0.33
40	Arg	1359.	A	B	.	.	.	.	-0.09	*	*	.	-0.26	0.51
	Ala	1360.	A	B	.	.	.	.	-0.09	*	*	.	0.38	0.77
	Leu	1361.	A	.	.	.	.	C	0.61	*	*	.	1.67	1.49
	Pro	1362.	.	.	.	.	T	C	1.20	*	*	F	2.86	1.49
	Pro	1363.	.	.	.	T	T	.	1.31	*	*	F	3.40	2.56
45	Asp	1364.	.	.	.	T	T	.	0.91	*	.	F	3.06	3.14
	Arg	1365.	.	.	.	T	T	.	0.69	.	.	F	2.42	2.13
	Gln	1366.	A	B	.	.	.	.	1.26	.	.	.	1.13	1.14
	Ala	1367.	A	B	.	.	.	.	1.43	.	.	.	0.19	1.07
	Trp	1368.	A	B	.	.	.	.	1.64	.	.	.	-0.60	0.74

	Leu	1369.	A	B	.	.	.	1.64	.	.	.	-0.60	0.74
	Tyr	1370.	A	B	.	.	.	1.50	*	.	.	-0.15	1.23
	His	1371.	A	B	.	.	.	1.61	.	.	.	-0.15	1.59
5	Glu	1372.	A	.	.	T	.	2.20	.	*	.	1.15	3.77
	Asp	1373.	A	.	.	T	.	2.53	.	*	F	1.30	4.02
	His	1374.	A	.	.	T	.	2.53	.	*	F	1.30	5.90
	Arg	1375.	A	.	.	T	.	2.19	.	*	F	1.30	2.81
	Asp	1376 A	A	.	.	.	.	1.63	.	*	F	0.90	1.70
10	Lys	1377 A	A	.	.	.	.	0.74	.	*	F	0.90	1.26
	Leu	1378 A	A	.	.	.	.	-0.07	*	*	.	0.60	0.45
	Ala	1379 A	A	.	.	.	.	0.08	*	*	.	-0.30	0.22
	Ala	1380.	A	B	.	.	.	-0.38	*	*	.	-0.30	0.22
	Ile	1381.	A	B	.	.	.	-0.41	*	*	.	-0.60	0.26
15	Leu	1382.	A	B	.	.	.	-1.06	.	*	.	-0.30	0.35
	Arg	1383.	A	B	.	.	.	-1.13	.	*	.	-0.60	0.35
	Gly	1384.	A	B	.	.	.	-0.43	.	.	.	-0.60	0.35
	His	1385.	A	B	.	.	.	0.16	.	.	.	0.30	0.82
	Met	1386.	A	B	.	.	.	0.19	.	.	.	0.30	0.67
20	Ile	1387.	A	B	.	.	.	1.00	.	*	.	-0.30	0.51
	Arg	1388.	A	B	.	.	.	0.30	*	.	.	0.30	0.64
	Asn	1389.	A	B	.	.	.	-0.17	*	.	.	0.30	0.66
	Val	1390.	A	B	.	.	.	-0.72	*	.	.	0.30	0.77
	Glu	1391.	A	B	.	.	.	-0.42	*	.	.	0.30	0.40
25	Ala	1392.	A	B	.	.	.	0.47	*	.	.	-0.30	0.33
	Leu	1393.	A	B	.	.	.	-0.46	*	.	.	0.30	0.75
	Ala	1394.	A	B	.	.	.	-0.67	*	.	.	0.30	0.36
	Ser	1395.	.	B	.	.	.	0.19	*	.	F	0.05	0.55
	Asp	1396.	.	B	.	.	.	-0.62	*	.	F	0.20	1.06
30	Leu	1397.	.	B	.	.	T	-0.38	*	.	F	0.25	0.87
	Pro	1398.	.	.	.	.	T	0.22	*	.	F	0.45	0.64
	Asn	1399.	.	.	.	T	T	0.00	.	*	F	0.65	0.59
	Leu	1400.	.	.	.	.	T	0.41	.	*	F	0.15	0.59
	Gly	1401.	.	.	.	.	T	0.10	.	.	F	0.45	0.75
35	Pro	1402.	.	B	.	.	T	0.31	.	.	F	0.25	0.67
	Leu	1403.	.	B	.	.	T	0.49	.	.	F	0.25	0.81
	Arg	1404.	.	B	.	.	T	0.14	.	.	F	0.40	1.11
	Thr	1405.	.	B	.	.	T	0.64	.	.	.	0.10	0.71
	Met	1406.	.	B	.	.	T	0.78	.	*	.	0.25	1.25
40	His	1407.	.	B	.	.	T	0.10	.	.	.	0.70	0.98
	Gly	1408.	.	B	.	.	T	0.61	*	*	F	-0.05	0.48
	Thr	1409.	.	.	.	.	.	-0.20	*	.	F	-0.05	0.65
	Pro	1410.	.	B	.	.	.	-0.19	.	.	F	-0.25	0.41
	Ile	1411.	.	.	.	T	.	-0.26	.	*	F	0.15	0.56
45	Ser	1412.	.	B	.	.	.	-0.52	*	.	.	-0.40	0.21
	Phe	1413.	.	B	.	.	.	-0.07	*	.	.	-0.06	0.18
	Ser	1414.	.	B	.	.	.	-0.07	.	*	.	0.58	0.50
	Cys	1415.	.	B	.	.	T	0.26	.	*	.	1.12	0.54
	Ser	1416.	.	.	.	T	T	0.93	.	*	F	2.76	1.22
	Arg	1417.	.	.	.	T	T	0.89	.	*	F	3.40	1.41



5	Thr	1418.	.	.	.	.	T	C	1.59	.	.	F	2.86	2.60
	Arg	1419.	.	.	.	.	T	C	1.08	.	*	F	2.52	3.36
	Pro	1420.	.	.	.	.	T	C	1.14	.	*	F	2.18	1.42
	Gly	1421.	.	.	.	T	T	.	0.59	.	*	F	1.59	0.97
	Glu	1422.	.	B	.	.	T	.	0.13	.	*	F	0.85	0.37
10	Leu	1423.	.	B	.	.	.	.	0.44	.	.	.	-0.10	0.24
	Met	1424.	.	B	.	.	.	.	0.33	.	.	.	0.50	0.41
	Val	1425.	.	B	.	.	.	.	0.54	.	.	.	0.80	0.40
	Gly	1426.	.	B	.	.	T	.	0.30	.	*	.	1.00	0.80
	Glu	1427 A	.	.	.	.	T	.	0.41	.	*	F	1.15	0.82
15	Asp	1428 A	.	.	.	.	T	.	0.33	*	*	F	1.30	2.17
	Asp	1429 A	.	.	.	.	T	.	0.08	*	*	F	1.30	1.54
	Ala	1430 A	.	.	B	.	.	.	0.93	*	*	F	0.75	0.66
	Arg	1431.	.	B	B	.	.	.	1.39	*	*	.	0.60	0.68
	Ile	1432.	.	B	B	.	.	.	1.36	*	*	.	0.60	0.80
20	Val	1433.	.	B	B	.	.	.	0.54	*	*	.	0.45	1.08
	Gln	1434.	.	B	B	.	.	.	0.33	*	*	.	0.30	0.45
	Arg	1435.	.	B	B	.	.	.	0.22	*	*	.	-0.15	1.00
	His	1436.	.	B	B	.	.	.	0.11	*	*	.	-0.45	1.17
	Leu	1437.	.	B	B	.	.	.	0.66	.	.	.	0.45	1.17
25	Pro	1438.	.	.	.	.	.	C	1.17	.	*	.	0.70	0.59
	Phe	1439.	.	.	.	T	T	.	0.36	.	.	.	0.50	0.43
	Glu	1440.	.	.	.	T	T	.	-0.34	.	.	F	0.35	0.43
	Gly	1441.	.	.	.	T	T	.	-0.56	.	*	F	0.65	0.28
	Gly	1442.	.	.	.	T	T	.	-0.09	.	*	F	0.35	0.51
30	Leu	1443.	.	.	.	.	.	C	-0.77	*	*	.	0.10	0.29
	Ala	1444.	.	.	.	.	.	C	-0.07	*	*	.	-0.20	0.21
	Tyr	1445.	.	B	.	.	.	.	-0.07	*	.	.	-0.40	0.35
	Gly	1446.	.	B	.	.	.	.	-0.53	*	.	.	-0.40	0.73
	Ile	1447.	A	B	.	.	.	.	-1.00	*	.	.	-0.60	0.59
35	Asp	1448.	A	B	.	.	.	.	-0.19	*	.	F	-0.45	0.31
	Gln	1449.	A	B	.	.	.	.	0.19	*	.	F	0.45	0.55
	Leu	1450.	A	B	.	.	.	.	0.22	*	.	F	0.60	1.21
	Leu	1451.	A	B	.	.	.	.	0.22	*	.	F	0.60	1.12
	Glu	1452.	A	B	.	.	.	.	0.30	*	.	F	0.07	0.64
40	Pro	1453.	.	.	.	.	T	C	-0.04	*	.	F	0.89	0.64
	Pro	1454.	.	.	.	T	T	.	-0.63	*	*	F	1.31	0.77
	Gly	1455.	.	.	.	T	T	.	0.29	*	*	F	2.13	0.45
	Leu	1456.	.	.	.	T	T	.	0.43	.	*	.	2.20	0.57
	Gly	1457.	.	.	.	.	T	C	0.43	.	*	.	1.18	0.20
45	Ala	1458.	.	B	.	.	T	.	0.61	.	*	.	1.36	0.33
	Arg	1459.	.	B	.	.	T	.	0.12	.	*	.	1.14	0.55
	Cys	1460.	.	B	.	.	T	.	0.47	.	*	.	0.92	0.48
	Asp	1461.	A	B	.	.	.	.	0.97	*	*	.	0.60	0.82
	His	1462.	A	B	.	.	.	.	1.42	*	*	.	0.60	0.60
	Phe	1463.	A	B	.	.	.	.	1.80	*	*	.	1.05	2.21
	Glu	1464.	A	B	.	.	.	.	0.88	*	.	F	1.50	2.04
	Thr	1465.	A	B	.	.	.	.	1.66	*	.	F	1.50	1.24
	Arg	1466.	.	B	.	.	.	.	0.84	*	*	F	2.30	2.80

5	Pro	1467.	.	.	.	T	.	.	0.88	*	*	F	3.00	1.33
	Leu	1468.	.	.	.	T	.	.	1.27	*	*	.	2.25	1.49
	Arg	1469.	.	.	.	T	.	.	0.60	*	*	.	1.95	1.10
	Leu	1470.	.	.	.	T	.	.	0.61	*	.	.	0.90	0.38
	Asn	1471.	.	.	.	T	T	.	-0.39	*	.	.	0.80	0.62
10	Thr	1472.	.	B	.	.	T	.	-0.84	.	*	.	0.10	0.22
	Cys	1473.	.	B	.	.	T	.	-0.38	*	*	.	-0.20	0.14
	Ser	1474.	.	B	.	.	T	.	-1.30	*	*	.	-0.20	0.09
	Ile	1475.	.	B	B	.	.	.	-0.49	.	.	.	-0.60	0.05
	Cys	1476.	.	B	B	.	.	.	-0.70	.	.	.	-0.30	0.16
15	Gly	1477.	.	.	B	T	.	.	-0.60	.	.	.	0.10	0.19
	Leu	1478.	.	.	.	T	.	.	-0.60	.	.	.	0.30	0.42
	Glu	1479.	.	.	.	.	.	C	-0.51	.	.	F	0.25	0.42
	Pro	1480.	.	.	.	.	.	C	0.38	.	.	F	0.85	0.65
	Pro	1481.	.	.	.	T	.	.	0.70	.	.	F	1.54	1.36
20	Cys	1482.	.	.	.	.	T	C	0.74	*	.	F	2.03	0.78
	Pro	1483.	.	.	.	T	T	.	1.56	*	.	F	2.27	0.67
	Glu	1484.	.	.	.	T	T	.	1.56	.	.	F	2.61	0.76
	Gly	1485.	.	.	.	T	T	.	1.77	.	.	F	3.40	2.44
	Ser	1486.	.	.	.	.	.	C	1.63	.	.	F	2.66	2.73
25	Gln	1487.	.	.	.	.	.	C	2.00	.	.	F	2.62	1.56
	Glu	1488.	.	.	.	T	.	.	2.00	.	.	F	2.78	2.12
	Gln	1489.	.	.	.	T	.	.	2.00	.	.	F	2.74	2.44
	Gly	1490.	.	.	.	.	.	C	1.76	.	.	F	2.50	2.44
	Ser	1491.	.	.	.	.	T	C	1.39	.	*	F	3.00	1.42
30	Pro	1492.	.	.	.	.	T	C	1.10	.	*	F	2.25	0.44
	Glu	1493.	.	.	.	T	T	.	1.21	*	*	F	1.55	0.47
	Ala	1494.	.	.	.	T	T	.	0.51	*	*	.	1.70	0.68
	Cys	1495.	.	.	.	T	.	.	0.61	*	*	.	0.60	0.38
	Trp	1496.	.	B	.	.	.	.	0.70	*	*	.	-0.40	0.35
35	Arg	1497.	.	B	.	.	.	.	0.96	*	*	.	-0.40	0.53
	Phe	1498.	.	B	.	.	.	.	0.26	*	*	.	-0.25	1.98
	Tyr	1499.	.	B	.	.	.	.	0.56	*	*	.	-0.25	1.63
	Pro	1500.	.	.	.	T	T	.	0.91	*	*	.	0.20	0.88
	Lys	1501.	.	.	.	T	T	.	0.90	*	*	.	0.35	1.46
40	Phe	1502.	.	.	.	T	T	.	0.58	*	*	F	0.50	1.25
	Trp	1503.	.	.	.	T	T	.	1.07	.	*	F	0.50	1.25
	Thr	1504.	.	.	.	.	.	C	0.50	.	*	F	-0.05	0.97
	Ser	1505.	.	.	.	.	T	C	0.68	.	*	F	0.15	0.92
	Pro	1506.	.	.	.	.	T	C	0.33	.	*	F	0.30	1.19
45	Pro	1507.	.	.	.	.	T	C	0.22	.	.	F	0.60	1.10
	Leu	1508.	.	.	.	.	T	C	0.17	.	.	F	0.15	0.68
	His	1509.	.	.	.	.	T	C	-0.33	*	*	.	0.00	0.44
	Ser	1510.	.	B	.	.	T	.	0.08	*	*	.	-0.20	0.23
	Leu	1511.	.	B	.	.	T	.	-0.01	*	.	.	0.10	0.55
	Gly	1512.	.	B	.	.	T	.	-0.66	*	*	.	0.10	0.54
	Leu	1513.	.	B	B	.	.	.	-0.13	*	.	.	-0.30	0.30
	Arg	1514.	.	B	B	.	.	.	-0.96	.	*	.	-0.60	0.38
	Ser	1515.	.	B	B	.	.	.	-0.69	.	*	.	-0.60	0.29

5	Val	1516.	.	B	B	.	.	.	-0.09	.	*	.	-0.60	0.47
	Trp	1517.	.	B	B	.	.	.	-0.04	.	*	.	-0.60	0.37
	Val	1518.	.	B	B	.	.	.	-0.04	*	.	.	-0.60	0.37
	His	1519.	.	B	.	.	T	.	-0.44	.	.	.	-0.20	0.42
	Pro	1520.	.	.	.	.	T	C	-0.49	.	*	.	0.00	0.42
10	Ser	1521.	.	.	.	T	T	.	0.48	.	*	F	0.35	0.55
	Leu	1522.	.	.	.	T	T	.	0.56	.	*	.	0.50	0.80
	Trp	1523.	.	.	.	T	.	.	1.41	.	*	.	0.30	0.80
	Gly	1524.	.	.	.	.	.	C	1.10	.	*	F	0.71	1.03
	Arg	1525.	.	.	.	.	.	C	0.50	.	*	F	1.02	1.24
15	Pro	1526.	.	.	.	T	T	.	0.46	*	*	F	1.58	0.97
	Gln	1527.	.	.	.	T	T	.	1.38	*	*	F	2.49	0.97
	Gly	1528.	.	.	.	T	T	.	1.32	*	*	F	3.10	0.97
	Leu	1529.	.	.	.	T	T	.	1.00	*	*	F	2.49	0.62
	Gly	1530.	.	.	.	T	T	.	0.86	*	*	F	2.46	0.19
20	Arg	1531.	.	.	.	T	T	.	1.18	*	*	F	1.83	0.26
	Gly	1532.	.	.	.	T	T	.	1.18	*	*	.	2.25	0.63
	Cys	1533.	.	.	.	T	T	.	0.86	*	*	.	2.67	1.02
	His	1534.	.	.	.	T	T	.	0.81	*	*	.	2.80	0.28
	Arg	1535.	.	B	.	.	T	.	0.84	*	*	.	1.22	0.21
25	Asn	1536.	.	B	.	.	T	.	0.42	*	*	.	0.94	0.56
	Cys	1537.	.	B	.	.	T	.	0.46	.	*	.	0.66	0.60
	Val	1538.	.	B	B	.	.	.	0.83	*	*	.	-0.02	0.44
	Thr	1539.	.	B	B	.	.	.	0.91	*	*	.	-0.60	0.29
	Thr	1540.	.	.	B	T	.	.	0.59	*	*	F	0.10	1.08
30	Thr	1541.	.	.	B	T	.	.	0.29	*	*	F	0.10	2.24
	Trp	1542.	.	.	B	T	.	.	0.29	.	*	F	0.40	2.08
	Lys	1543.	.	.	.	.	T	C	0.48	.	*	F	0.45	0.77
	Pro	1544.	.	.	.	T	T	.	0.58	.	.	F	0.65	0.29
	Ser	1545.	.	.	.	T	T	.	0.54	.	.	.	0.50	0.42
35	Cys	1546.	.	.	.	T	T	.	0.82	.	.	.	1.10	0.21
	Cys	1547.	.	B	.	.	T	.	0.87	.	.	.	0.34	0.18
	Pro	1548.	.	.	.	T	T	.	0.48	.	.	.	0.68	0.21
	Gly	1549.	.	.	.	T	T	.	0.39	.	.	.	0.92	0.40
	His	1550.	.	.	.	T	T	.	0.69	.	.	F	1.31	0.99
40	Tyr	1551.	.	.	.	T	.	.	0.69	.	.	F	2.40	1.11
	Gly	1552.	.	.	.	T	T	.	1.36	.	.	F	1.61	0.60
	Ser	1553.	.	.	.	T	T	.	0.98	.	.	F	1.37	0.77
	Glu	1554.	.	B	.	.	T	.	0.66	.	.	F	0.73	0.49
	Cys	1555.	.	B	.	.	T	.	0.48	.	.	.	0.94	0.27
45	Gln	1556.	.	B	.	.	.	.	0.38	.	.	.	0.50	0.31
	Ala	1557.	.	B	.	.	.	.	0.38	.	.	.	0.50	0.18
	Cys	1558.	.	B	.	.	T	.	0.47	.	.	.	0.10	0.33
	Pro	1559.	.	.	.	T	T	.	0.17	.	.	F	0.65	0.29
	Gly	1560.	.	.	.	T	T	.	0.53	.	.	F	0.65	0.39
	Gly	1561.	.	.	.	.	T	C	0.32	.	.	F	0.45	0.96
	Pro	1562.	.	.	.	T	.	.	0.24	.	.	F	1.39	0.96
	Ser	1563.	.	.	.	.	.	C	0.61	.	.	F	0.93	0.52
	Ser	1564.	.	B	.	.	T	.	0.82	.	.	F	1.27	0.71

5	Pro	1565.	.	B	.	.	T	.	1.28	.	.	F	2.21	0.76
	Cys	1566.	.	.	.	.	T	T	1.28	.	.	F	3.40	1.12
	Ser	1567.	.	.	.	.	T	T	0.63	.	.	F	2.91	0.82
	Asp	1568.	.	.	.	.	T	T	0.27	.	.	F	2.57	0.40
	Arg	1569.	.	B	.	.	.	T	-0.03	.	.	F	1.53	0.40
10	Gly	1570.	.	B	.	.	.	T	0.18	.	.	.	1.04	0.29
	Val	1571.	.	B	.	.	.	T	0.50	.	.	.	1.00	0.29
	Cys	1572.	.	B	.	.	.	T	0.20	.	.	.	0.91	0.15
	Met	1573.	.	B	.	.	.	T	-0.10	.	.	.	0.52	0.15
	Asp	1574.	.	B	.	.	.	T	-0.56	.	.	.	0.73	0.27
15	Gly	1575.	.	.	.	.	T	T	-0.51	.	.	F	1.49	0.49
	Met	1576.	.	.	.	.	T	.	0.00	.	.	F	2.10	0.67
	Ser	1577.	.	.	.	.	T	.	0.67	.	.	F	1.89	0.39
	Gly	1578.	.	.	.	.	T	T	0.60	*	.	F	1.28	0.69
	Ser	1579.	.	.	.	.	T	T	-0.21	*	.	F	1.07	0.37
20	Gly	1580.	.	.	.	.	T	T	-0.53	*	*	F	0.86	0.23
	Gln	1581.	.	B	.	.	.	T	0.18	*	*	F	-0.05	0.12
	Cys	1582.	.	B	.	.	.	.	0.18	*	*	.	-0.10	0.18
	Leu	1583.	.	B	.	.	.	.	0.18	*	*	.	-0.10	0.25
	Cys	1584.	.	B	.	.	.	T	-0.22	*	*	.	0.10	0.14
25	Arg	1585.	.	B	.	.	.	T	-0.47	*	*	.	-0.20	0.23
	Ser	1586.	.	.	.	.	T	T	-0.81	*	*	F	0.65	0.28
	Gly	1587.	.	.	.	.	T	T	-0.46	.	*	F	0.65	0.52
	Phe	1588.	.	.	.	.	T	.	-0.23	.	.	F	0.45	0.38
	Ala	1589.	.	.	.	.	T	.	-0.23	.	*	.	0.00	0.29
30	Gly	1590.	.	.	.	.	T	.	-0.34	.	*	.	0.00	0.16
	Thr	1591.	A	B	.	.	.	.	-0.86	.	.	.	-0.30	0.31
	Ala	1592.	A	B	.	.	.	.	-1.18	.	.	.	-0.30	0.25
	Cys	1593.	A	B	.	.	.	.	-1.07	.	.	.	-0.30	0.14
	Glu	1594.	A	B	.	.	.	.	-0.69	.	.	.	-0.30	0.10
35	Leu	1595.	A	B	.	.	.	.	-0.69	.	.	.	-0.30	0.15
	Cys	1596.	A	B	.	.	.	.	-0.97	.	.	.	-0.30	0.27
	Ala	1597.	.	B	.	.	.	T	-1.08	.	.	.	0.10	0.16
	Pro	1598.	.	.	.	.	T	T	-0.76	.	*	.	0.20	0.17
	Gly	1599.	.	.	.	.	T	T	-0.97	.	.	.	0.20	0.31
40	Ala	1600.	.	.	.	.	T	T	-0.19	.	.	.	0.20	0.47
	Phe	1601.	.	.	.	.	T	.	-0.19	.	.	.	0.00	0.41
	Gly	1602.	.	.	.	.	.	T	0.40	.	*	.	0.00	0.22
	Pro	1603.	.	.	.	.	T	T	0.02	.	.	.	0.20	0.38
	His	1604.	.	.	.	.	T	T	-0.30	*	.	.	0.20	0.45
45	Cys	1605.	.	.	.	.	T	T	0.40	*	.	.	0.20	0.24
	Gln	1606.	A	.	.	.	T	.	0.43	.	.	.	0.70	0.31
	Ala	1607.	A	.	.	.	T	.	0.47	.	*	.	0.10	0.12
	Cys	1608.	A	B	B	.	.	.	-0.18	*	*	.	-0.30	0.33
	Arg	1609.	A	B	B	.	.	.	-0.18	*	*	.	-0.30	0.14
	Cys	1610.	.	B	B	.	.	.	0.14	.	*	.	-0.30	0.19
	Thr	1611.	.	B	B	.	.	.	0.26	.	*	.	-0.30	0.35
	Val	1612.	.	B	B	.	.	.	0.18	.	*	.	0.30	0.35
	His	1613.	.	B	B	.	.	.	0.84	.	*	.	-0.30	0.35

5	Gly	1614.	.	.	B	T	.	.	0.73	.	*	.	0.70	0.40
	Arg	1615.	.	B	.	.	.	.	1.06	*	*	F	0.95	0.94
	Cys	1616.	.	B	.	.	T	.	0.56	*	*	F	1.42	0.68
	Asp	1617.	.	B	.	.	T	.	1.07	.	*	F	1.69	0.57
	Glu	1618.	.	B	.	.	T	.	0.76	.	*	F	1.96	0.29
10	Gly	1619.	.	.	.	T	T	.	0.80	*	*	F	2.33	0.53
	Leu	1620.	.	.	.	T	.	.	0.34	*	*	F	2.70	0.43
	Gly	1621.	.	.	.	T	.	.	0.71	.	.	F	2.13	0.24
	Gly	1622.	.	.	.	T	T	.	0.04	.	.	F	1.46	0.33
	Ser	1623.	.	.	.	T	T	.	-0.66	.	.	F	1.19	0.21
15	Gly	1624.	.	.	.	T	T	.	-0.98	*	.	F	0.62	0.19
	Ser	1625.	.	B	.	.	T	.	-0.17	*	.	F	-0.05	0.10
	Cys	1626.	.	B	.	.	.	.	0.18	.	.	.	-0.10	0.13
	Phe	1627.	.	B	.	.	.	.	0.18	.	.	.	0.50	0.22
	Cys	1628.	.	B	.	.	.	.	0.19	.	.	.	0.75	0.16
20	Asp	1629.	.	.	.	T	T	.	0.22	*	.	.	1.00	0.32
	Glu	1630.	.	.	.	T	T	.	0.18	.	.	F	1.40	0.53
	Gly	1631.	.	.	.	T	T	.	0.63	*	.	F	2.25	0.99
	Trp	1632.	.	.	.	T	T	.	1.44	*	.	F	2.50	0.91
	Thr	1633.	.	.	.	.	.	C	1.44	*	*	F	2.00	1.03
25	Gly	1634.	.	.	.	.	T	C	1.44	*	*	F	1.20	0.56
	Pro	1635.	.	.	.	.	T	C	0.59	*	*	F	1.55	0.92
	Arg	1636.	.	.	.	T	T	.	0.93	*	*	F	1.50	0.47
	Cys	1637.	.	B	.	.	T	.	0.41	.	*	.	1.00	0.83
	Glu	1638.	A	B	.	.	.	.	0.72	.	*	.	0.30	0.44
30	Val	1639.	A	B	.	.	.	.	0.26	.	*	.	0.60	0.39
	Gln	1640.	A	B	.	.	.	.	0.47	.	*	.	0.30	0.60
	Leu	1641.	A	B	.	.	.	.	0.14	.	*	.	0.30	0.60
	Glu	1642.	A	B	.	.	.	.	-0.04	.	*	.	-0.15	1.25
	Leu	1643.	A	B	.	.	.	.	-0.71	.	*	.	-0.30	0.54
35	Gln	1644.	A	B	.	.	.	.	-0.17	.	*	.	-0.60	0.35
	Pro	1645.	A	.	.	T	.	.	-0.38	.	*	.	0.10	0.29
	Val	1646.	.	.	B	T	.	.	0.22	.	*	.	-0.20	0.55
	Cys	1647.	.	.	B	T	.	.	-0.44	.	.	.	0.10	0.49
	Thr	1648.	.	B	B	.	.	.	-0.22	.	.	.	-0.60	0.17
40	Pro	1649.	.	.	.	.	T	C	-0.43	.	.	F	0.15	0.23
	Pro	1650.	.	.	.	T	T	.	-0.22	.	.	F	0.35	0.66
	Cys	1651.	.	.	.	T	T	.	0.04	.	.	.	1.10	0.79
	Ala	1652.	.	B	.	.	T	.	-0.14	.	.	.	0.70	0.52
	Pro	1653.	A	B	.	.	.	.	-0.50	*	*	.	-0.30	0.25
45	Glu	1654.	A	B	.	.	.	.	-0.18	*	*	.	-0.30	0.25
	Ala	1655.	A	B	.	.	.	.	-0.56	*	*	.	0.52	0.48
	Val	1656.	A	B	.	.	.	.	-0.23	*	.	.	0.74	0.32
	Cys	1657.	.	B	.	.	T	.	0.36	*	.	.	1.36	0.18
	Arg	1658.	.	.	.	T	T	.	0.27	*	*	.	1.38	0.29
	Ala	1659.	.	.	.	T	T	.	-0.40	*	*	.	2.20	0.52
	Gly	1660.	.	.	.	T	T	.	0.19	*	*	F	2.13	0.52
	Asn	1661.	.	.	.	T	T	.	0.38	*	.	F	2.21	0.46
	Ser	1662.	.	.	.	T	T	.	0.74	*	*	F	1.69	0.24

5	Cys	1663.	.	B	.	.	T	.	-0.18	*	*	.	0.92	0.33
	Glu	1664.	.	B	.	.	T	.	0.07	.	.	.	0.10	0.17
	Cys	1665.	.	B	.	.	T	.	0.17	.	.	.	0.10	0.12
	Ser	1666.	.	B	.	.	T	.	0.17	.	*	.	-0.20	0.36
	Leu	1667.	.	B	.	.	T	.	0.12	.	*	.	1.04	0.36
10	Gly	1668.	.	.	.	T	T	.	0.79	.	*	.	1.18	0.67
	Tyr	1669.	.	.	.	T	.	.	0.44	.	*	.	1.92	0.84
	Glu	1670.	.	.	.	T	.	.	1.22	*	*	F	2.56	1.01
	Gly	1671.	.	.	.	T	T	.	0.67	.	*	F	3.40	1.99
	Asp	1672.	.	.	.	T	T	.	0.81	.	*	F	2.91	0.94
15	Gly	1673.	.	.	.	T	T	.	0.84	*	*	F	2.57	0.29
	Arg	1674.	.	B	.	.	T	.	0.23	*	*	F	1.53	0.43
	Val	1675.	.	B	B	.	.	.	-0.36	*	*	.	0.64	0.19
	Cys	1676.	.	B	B	.	.	.	-0.01	.	*	.	-0.30	0.19
	Thr	1677.	.	B	B	.	.	.	-0.82	.	*	.	0.30	0.16
20	Val	1678.	.	B	B	.	.	.	-1.14	.	*	.	-0.60	0.18
	Ala	1679.	.	B	B	.	.	.	-1.26	*	*	.	-0.60	0.18
	Asp	1680.	.	B	B	.	.	.	-0.40	*	.	.	-0.30	0.22
	Leu	1681.	.	B	.	.	.	.	-0.08	*	.	.	0.50	0.49
	Cys	1682.	.	B	.	.	T	.	0.20	*	.	.	0.95	0.48
25	Gln	1683.	.	B	.	.	T	.	0.71	*	.	.	1.20	0.39
	Asp	1684.	.	.	.	T	T	.	0.96	*	*	F	1.40	0.47
	Gly	1685.	.	.	.	T	T	.	0.29	*	.	F	2.25	0.87
	His	1686.	.	.	.	T	T	.	0.80	*	.	F	2.50	0.27
	Gly	1687.	.	.	.	T	T	.	1.47	.	.	F	2.25	0.22
30	Gly	1688.	.	.	.	T	T	.	1.43	.	.	F	2.00	0.38
	Cys	1689.	.	.	.	T	T	.	0.84	.	.	F	1.97	0.38
	Ser	1690.	.	B	.	T	.	.	1.19	.	.	F	1.74	0.39
	Glu	1691.	.	B	.	.	.	.	0.56	.	.	.	1.16	0.63
	His	1692.	.	.	.	T	T	.	0.60	.	.	.	1.98	0.63
35	Ala	1693.	.	.	.	T	T	.	0.94	.	.	.	2.20	0.63
	Asn	1694.	.	.	.	T	T	.	0.76	.	.	.	1.98	0.63
	Cys	1695.	.	.	.	T	T	.	0.71	.	.	.	0.86	0.34
	Ser	1696.	.	.	B	T	.	.	0.40	.	.	.	0.54	0.34
	Gln	1697.	.	.	B	T	.	.	-0.17	.	.	F	0.47	0.30
40	Val	1698.	.	.	B	T	.	.	-0.43	.	.	F	-0.05	0.56
	Gly	1699.	.	B	B	.	.	.	-0.74	.	.	F	-0.45	0.31
	Thr	1700.	.	B	B	.	.	.	-0.74	*	.	.	-0.60	0.26
	Met	1701.	.	B	B	.	.	.	-0.76	*	.	.	-0.60	0.19
	Val	1702.	.	B	B	.	.	.	-1.42	.	.	.	-0.60	0.27
45	Thr	1703.	.	B	B	.	.	.	-1.38	.	.	.	-0.60	0.10
	Cys	1704.	.	B	B	.	.	.	-1.24	.	.	.	-0.60	0.08
	Thr	1705.	.	B	B	.	.	.	-0.93	.	.	.	-0.60	0.17
	Cys	1706.	.	B	B	.	.	.	-0.58	.	.	.	0.04	0.20
	Leu	1707.	.	B	.	.	T	.	0.28	.	.	.	0.48	0.59
	Pro	1708.	.	B	.	.	T	.	0.24	.	*	F	1.87	0.71
	Asp	1709.	.	.	.	T	T	.	0.91	.	*	F	2.76	1.31
	Tyr	1710.	.	.	.	T	T	.	0.88	.	.	F	3.40	2.65
	Glu	1711.	.	.	.	T	.	.	1.26	.	.	F	2.86	1.70

5	Gly	1712.	.	.	.	T	T	.	1.77	.	.	F	2.42	1.07
	Asp	1713.	.	.	.	T	T	.	1.31	.	*	F	1.93	0.91
	Gly	1714.	.	.	.	T	T	.	1.42	.	*	F	1.59	0.28
	Trp	1715.	.	.	.	T	T	.	1.08	.	*	.	1.10	0.56
	Ser	1716.	.	B	.	.	.	.	1.19	*	*	.	0.50	0.34
10	Cys	1717.	.	.	.	T	.	.	1.53	*	*	.	0.90	0.67
	Arg	1718.	.	.	.	T	.	.	1.32	*	*	.	1.39	1.03
	Ala	1719.	.	.	.	T	.	.	1.00	.	*	F	2.18	1.18
	Arg	1720.	.	.	.	T	.	.	0.98	*	*	F	2.52	1.18
	Asn	1721.	.	.	.	.	T	C	1.28	*	*	F	2.71	0.87
15	Pro	1722.	.	.	.	T	T	.	1.60	*	*	F	3.40	1.44
	Cys	1723.	.	.	.	T	T	.	1.46	*	*	F	2.91	0.73
	Thr	1724.	.	.	.	T	T	.	2.16	*	.	F	2.58	0.62
	Asp	1725.	.	.	.	T	.	.	1.70	*	.	F	2.65	0.78
	Gly	1726.	.	.	.	T	.	.	1.36	*	.	F	2.77	1.44
20	His	1727.	.	.	.	T	T	.	0.90	*	.	F	2.79	0.99
	Arg	1728.	.	.	.	T	T	.	1.27	*	.	F	3.10	0.32
	Gly	1729.	.	.	.	T	T	.	1.58	*	.	F	2.49	0.43
	Gly	1730.	.	.	.	T	T	.	1.54	.	.	F	2.48	0.55
	Cys	1731.	.	.	.	T	.	.	1.30	.	.	F	1.97	0.38
25	Ser	1732.	.	B	.	.	.	.	1.33	.	*	F	0.96	0.39
	Glu	1733.	.	B	.	.	.	.	0.56	*	*	.	0.50	0.63
	His	1734.	.	B	.	.	T	.	0.09	.	.	.	0.70	0.63
	Ala	1735.	.	B	.	.	T	.	0.13	*	.	.	0.10	0.39
	Asn	1736.	.	B	.	.	T	.	0.49	*	.	.	0.10	0.30
30	Cys	1737.	.	B	.	.	T	.	0.44	*	.	.	-0.20	0.32
	Leu	1738.	.	B	.	.	.	.	-0.37	*	.	.	-0.40	0.31
	Ser	1739.	.	.	.	T	T	.	-0.33	*	.	F	0.69	0.16
	Thr	1740.	.	.	.	T	T	.	-0.06	.	*	F	1.03	0.48
	Gly	1741.	.	.	.	T	T	.	0.06	.	.	F	1.37	0.84
35	Leu	1742.	.	.	.	T	T	.	0.83	.	.	F	2.76	1.23
	Asn	1743.	.	.	.	T	T	.	0.98	.	*	F	3.40	1.67
	Thr	1744.	.	.	.	T	T	.	1.28	.	.	F	2.61	0.90
	Arg	1745.	.	.	.	T	T	.	0.92	.	.	F	2.72	1.89
	Arg	1746.	.	B	.	.	T	.	1.23	.	.	F	1.83	0.63
40	Cys	1747.	.	B	.	.	.	.	1.46	.	.	.	1.14	0.60
	Glu	1748.	.	B	.	.	.	.	1.11	*	.	.	0.80	0.31
	Cys	1749.	.	B	.	.	.	.	1.18	*	.	.	0.50	0.16
	His	1750.	.	B	.	.	T	.	0.21	*	.	.	0.10	0.45
	Ala	1751.	.	B	.	.	T	.	-0.24	*	*	.	-0.20	0.19
45	Gly	1752.	.	.	.	T	T	.	0.42	.	.	.	0.20	0.36
	Tyr	1753.	.	.	.	T	T	.	0.08	.	.	.	0.50	0.44
	Val	1754.	.	.	.	T	.	.	-0.07	*	.	.	0.30	0.43
	Gly	1755.	.	.	.	T	T	.	-0.03	*	.	.	0.50	0.36
	Asp	1756.	.	.	.	T	T	.	-0.11	*	.	.	0.50	0.40
	Gly	1757.	.	B	.	.	T	.	-0.58	*	.	.	0.10	0.29
	Leu	1758.	.	B	.	.	T	.	-0.33	*	.	.	0.10	0.24
	Gln	1759.	A	B	.	.	.	.	0.52	*	.	.	0.30	0.25
	Cys	1760.	A	B	.	.	.	.	0.57	*	.	.	0.60	0.43

	Leu	1761.	A	B	.	.	.	0.57	*	.	.	0.90	0.71
	Glu	1762.	A	B	.	.	.	0.70	*	.	F	1.65	0.71
	Glu	1763.	A	.	.	T	.	1.30	*	.	F	2.50	2.03
	Ser	1764.	.	.	.	T	.	0.44	*	.	F	3.00	3.82
5	Glu	1765.	.	.	.	.	C	1.11	*	.	F	2.50	1.64
	Pro	1766.	.	.	.	.	C	2.03	*	.	F	2.20	1.58
	Pro	1767.	.	.	.	T	.	1.37	*	.	F	2.10	2.30
	Val	1768.	.	.	.	T	.	0.56	*	.	F	1.65	0.71
	Asp	1769.	.	B	.	.	.	0.51	*	.	F	0.65	0.38
10	Arg	1770.	.	B	.	.	.	0.51	*	.	F	0.65	0.24
	Cys	1771.	.	B	.	.	.	0.51	*	.	.	0.50	0.57
	Leu	1772.	.	.	.	T	.	0.51	*	.	F	1.05	0.53
	Gly	1773.	.	.	.	T	.	1.16	*	.	F	1.05	0.42
	Gln	1774.	.	.	.	.	C	0.49	*	.	F	0.62	1.20
15	Pro	1775.	.	.	.	.	T	0.34	*	*	F	0.89	0.78
	Pro	1776.	.	.	.	.	T	0.71	.	.	F	1.26	1.07
	Pro	1777.	.	.	.	T	T	1.52	.	.	F	1.53	0.83
	Cys	1778.	.	.	.	T	T	1.28	.	.	.	2.20	0.89
	His	1779.	.	.	.	T	T	0.68	.	.	.	1.98	0.58
20	Ser	1780.	.	B	.	.	T	0.22	.	.	.	0.76	0.37
	Asp	1781.	.	B	.	.	T	0.12	.	.	.	0.54	0.37
	Ala	1782.	.	B	.	.	T	0.33	.	.	.	0.32	0.40
	Met	1783.	.	B	.	.	.	0.19	.	.	.	0.50	0.49
	Cys	1784.	.	B	.	.	T	0.19	.	*	.	0.70	0.24
25	Thr	1785.	.	B	.	.	T	-0.21	.	*	.	0.10	0.33
	Asp	1786 A	.	.	.	.	T	-0.21	.	*	.	-0.20	0.29
	Leu	1787 A	.	.	.	.	T	0.38	.	*	.	-0.20	0.93
	His	1788 A	A	.	.	.	.	1.02	.	*	.	0.45	1.12
	Phe	1789 A	A	.	.	.	.	1.80	*	*	.	0.75	1.34
30	Gln	1790 A	A	.	.	.	.	1.52	*	*	F	0.90	3.17
	Glu	1791 A	A	.	.	.	.	1.18	.	*	F	0.90	2.36
	Lys	1792.	A	.	.	T	.	1.13	.	.	F	1.30	2.69
	Arg	1793.	A	.	.	T	.	0.47	.	.	F	1.30	1.15
	Ala	1794.	A	.	.	T	.	1.13	.	.	F	1.15	0.58
35	Gly	1795.	A	.	.	T	.	0.32	.	.	.	0.70	0.39
	Val	1796.	A	B	.	.	.	0.32	.	*	.	-0.60	0.17
	Phe	1797.	A	B	.	.	.	-0.31	.	*	.	-0.60	0.28
	His	1798.	A	B	.	.	.	-0.73	.	*	.	-0.60	0.29
	Leu	1799.	A	B	.	.	.	-0.44	.	.	.	-0.60	0.56
40	Gln	1800.	A	B	.	.	.	-0.44	.	*	.	-0.60	0.87
	Ala	1801.	A	.	.	T	C	0.20	.	.	F	0.25	0.63
	Thr	1802.	A	.	.	T	.	0.66	.	*	F	0.40	1.19
	Ser	1803.	A	.	.	.	C	0.34	.	*	F	0.20	1.07
	Gly	1804.	.	.	.	.	T	0.34	.	*	F	0.30	1.05
45	Pro	1805.	.	.	.	T	T	0.34	.	*	F	0.35	0.60
	Tyr	1806.	.	.	.	T	T	0.23	.	*	F	0.35	0.72
	Gly	1807.	.	.	.	.	T	0.24	.	*	.	0.00	0.63
	Leu	1808.	.	.	.	.	C	0.54	.	.	.	-0.20	0.55
	Asn	1809.	A	B	.	.	.	0.30	.	.	.	-0.60	0.60



5	Phe	1810.	A	B	.	.	.	0.51	.	.	.	-0.30	0.62
	Ser	1811.	A	B	.	.	.	0.17	.	.	.	0.45	1.30
	Glu	1812 A	A	.	.	.	.	-0.08	.	.	F	0.45	0.81
	Ala	1813 A	A	.	.	.	.	0.07	.	*	.	0.30	0.95
	Glu	1814 A	A	.	.	.	.	0.07	.	*	.	0.60	0.38
10	Ala	1815 A	A	.	.	.	.	0.18	.	*	.	0.60	0.38
	Ala	1816 A	A	.	.	.	.	0.48	.	*	.	0.30	0.38
	Cys	1817 A	A	.	.	.	.	0.13	.	*	.	0.60	0.38
	Glu	1818 A	A	.	.	.	.	0.13	.	*	.	0.30	0.37
	Ala	1819 A	A	.	.	.	.	-0.72	.	*	.	0.30	0.37
15	Gln	1820 A	A	.	.	.	.	-0.94	.	*	.	-0.30	0.52
	Gly	1821 A	A	.	.	.	.	-0.94	.	.	.	-0.30	0.25
	Ala	1822.	A	B	.	.	.	-0.58	.	*	.	-0.60	0.25
	Val	1823.	A	B	.	.	.	-1.28	.	*	.	-0.60	0.19
	Leu	1824.	A	B	.	.	.	-0.90	.	.	.	-0.60	0.17
20	Ala	1825.	A	B	.	.	.	-0.90	.	.	.	-0.60	0.25
	Ser	1826.	A	B	.	.	.	-1.37	.	.	.	-0.60	0.59
	Phe	1827.	.	B	.	.	.	-1.08	.	.	.	-0.40	0.59
	Pro	1828.	.	.	.	.	C	-0.81	.	.	.	-0.20	0.79
	Gln	1829.	A	.	.	.	C	-0.59	.	.	.	-0.40	0.59
25	Leu	1830.	A	B	.	.	.	0.00	.	.	.	-0.60	0.69
	Ser	1831.	A	.	.	.	C	0.30	.	.	.	-0.10	0.78
	Ala	1832.	A	B	.	.	.	0.19	.	.	.	-0.30	0.78
	Ala	1833.	A	B	.	.	.	0.06	.	*	.	-0.60	0.78
	Gln	1834.	A	B	.	.	.	-0.64	.	*	.	-0.30	0.57
30	Gln	1835.	A	B	.	.	.	0.13	*	*	.	-0.60	0.49
	Leu	1836.	A	B	.	.	.	-0.38	*	*	.	-0.60	0.66
	Gly	1837.	A	B	.	.	.	-0.46	.	*	.	-0.60	0.31
	Phe	1838.	A	B	.	.	.	-0.68	.	*	.	-0.60	0.10
	His	1839.	A	B	.	.	.	-1.28	.	*	.	-0.60	0.10
35	Leu	1840.	A	B	.	.	.	-1.62	.	*	.	-0.60	0.10
	Cys	1841.	A	B	.	.	.	-1.10	.	*	.	-0.60	0.11
	Leu	1842.	A	B	.	.	.	-1.57	.	.	.	-0.60	0.09
	Met	1843.	A	B	.	.	.	-1.46	.	*	.	-0.60	0.09
	Gly	1844.	A	B	.	.	.	-1.42	.	.	.	-0.60	0.16
40	Trp	1845.	A	B	.	.	.	-0.96	.	.	.	-0.60	0.32
	Leu	1846.	A	.	.	.	C	-0.59	.	.	.	-0.40	0.32
	Ala	1847.	A	.	.	.	C	-0.09	.	.	.	-0.40	0.43
	Asn	1848.	.	.	.	.	T	-0.08	.	.	F	0.15	0.59
	Gly	1849.	.	.	.	T	T	0.23	.	.	F	0.65	0.72
45	Ser	1850.	.	.	.	.	T	0.31	.	.	F	0.45	0.97
	Thr	1851.	.	.	.	.	T	0.27	.	.	F	0.45	0.93
	Ala	1852.	.	.	.	.	C	0.00	.	.	F	0.25	0.70
	His	1853.	.	B	B	.	.	-0.70	.	.	.	-0.60	0.39
	Pro	1854.	.	B	B	.	.	-0.57	.	.	.	-0.60	0.23
	Val	1855.	.	B	B	.	.	-1.12	.	.	.	-0.60	0.36
	Val	1856.	.	B	B	.	.	-1.40	*	.	.	-0.60	0.19
	Phe	1857.	.	B	B	.	.	-0.81	*	.	.	-0.60	0.13
	Pro	1858.	.	B	B	.	.	-1.44	*	.	.	-0.60	0.29

	Val	1859.	.	B	B	.	.	.	-1.58	*	.	.	-0.29	0.21
	Ala	1860.	.	B	B	.	.	.	-0.72	*	.	.	0.32	0.24
	Asp	1861.	.	.	B	T	.	.	-0.21	.	*	.	1.63	0.24
5	Cys	1862.	.	.	.	T	T	.	0.60	.	*	.	2.34	0.33
	Gly	1863.	.	.	.	T	T	.	-0.04	.	*	F	3.10	0.63
	Asn	1864.	.	.	.	T	T	.	0.47	.	*	F	2.79	0.28
	Gly	1865.	.	.	.	T	T	.	0.17	.	*	F	2.18	0.52
	Arg	1866.	.	B	B	.	.	.	-0.69	.	*	F	0.47	0.37
10	Val	1867.	.	B	B	.	.	.	-0.32	.	*	.	0.01	0.17
	Gly	1868.	.	B	B	.	.	.	-0.79	.	*	.	-0.30	0.23
	Ile	1869.	.	B	B	.	.	.	-1.13	.	*	.	-0.60	0.10
	Val	1870.	.	B	B	.	.	.	-1.38	.	*	.	-0.60	0.13
	Ser	1871.	.	B	.	.	.	.	-1.38	.	*	.	-0.40	0.13
	Leu	1872.	.	B	.	.	.	.	-0.48	.	*	.	-0.10	0.37
15	Gly	1873.	.	B	.	.	.	.	-0.13	.	*	.	0.50	0.99
	Ala	1874.	.	.	.	.	.	C	-0.06	*	*	F	1.30	1.19
	Arg	1875.	.	.	.	.	.	C	0.50	*	*	F	1.00	1.19
	Lys	1876.	.	.	.	.	.	C	0.80	.	*	F	1.60	1.61
20	Asn	1877.	.	.	.	.	.	C	1.72	.	*	F	1.90	2.76
	Leu	1878.	.	.	.	.	.	C	1.78	.	*	F	2.20	2.76
	Ser	1879.	.	B	.	.	.	.	2.37	.	*	F	2.30	1.45
	Glu	1880.	.	B	.	T	.	.	1.67	.	*	F	3.00	1.51
	Arg	1881.	.	.	.	T	.	.	1.38	*	*	F	2.70	1.85
25	Trp	1882.	.	.	.	T	.	.	0.71	.	*	.	1.95	2.16
	Asp	1883.	.	.	.	T	T	.	0.82	*	*	.	1.70	0.67
	Ala	1884.	.	.	.	T	T	.	1.23	*	*	.	0.50	0.30
	Tyr	1885.	.	B	.	.	T	.	0.38	*	*	.	-0.20	0.55
	Cys	1886.	.	B	.	.	T	.	0.27	*	*	.	0.10	0.24
30	Phe	1887.	.	B	B	.	.	.	0.56	*	.	.	-0.60	0.42
	Arg	1888.	.	B	B	.	.	.	-0.30	*	*	.	-0.30	0.45
	Val	1889.	.	B	B	.	.	.	-0.30	.	*	.	-0.30	0.62
	Gln	1890.	.	B	B	.	.	.	-0.72	*	*	.	0.30	0.72
	Asp	1891.	.	B	B	.	.	.	0.06	*	*	.	0.30	0.20
35	Val	1892.	.	B	B	.	.	.	0.09	*	*	.	0.30	0.52
	Ala	1893.	.	B	B	.	.	.	0.09	*	*	.	0.55	0.16
	Cys	1894.	.	B	B	.	.	.	0.94	*	*	.	1.10	0.19
	Arg	1895.	.	B	B	.	.	.	0.60	*	*	.	1.05	0.41
	Cys	1896.	.	B	.	.	T	.	-0.10	*	*	.	2.00	0.40
40	Arg	1897.	.	.	.	T	T	.	-0.10	*	*	F	2.50	0.65
	Asn	1898.	.	.	.	T	T	.	0.14	.	*	F	2.25	0.25
	Gly	1899.	.	.	.	T	T	.	0.81	.	*	F	1.40	0.45
	Phe	1900.	.	B	.	.	.	.	0.36	.	*	.	1.00	0.39
	Val	1901.	.	B	.	.	T	.	0.13	.	.	.	0.35	0.24
45	Gly	1902.	.	.	.	T	T	.	-0.28	.	.	F	0.20	0.17
	Asp	1903.	.	B	.	.	T	.	-0.59	.	.	F	0.25	0.26
	Gly	1904.	.	B	.	.	T	.	-0.91	*	.	F	0.25	0.51
	Ile	1905.	.	B	B	.	.	.	-0.21	*	.	F	0.45	0.28
	Ser	1906.	.	B	B	.	.	.	0.30	*	*	F	0.45	0.27
	Thr	1907.	.	B	B	.	.	.	0.69	*	*	F	0.02	0.27

	Cys	1908.	.	B	.	.	T	.	-0.12	*	.	F	1.19	0.76
	Asn	1909.	.	.	.	T	T	.	-0.59	*	.	F	1.76	0.47
	Gly	1910.	.	.	.	T	T	.	0.30	*	.	F	1.33	0.27
	Lys	1911.	.	B	.	.	T	.	-0.26	*	.	F	1.70	0.83
5	Leu	1912.	A	B	.	.	.	.	-0.76	*	.	F	1.13	0.38
	Leu	1913.	A	B	.	.	.	.	-0.68	.	.	.	0.21	0.32
	Asp	1914.	A	B	.	.	.	.	-1.27	.	.	.	0.04	0.16
	Val	1915.	A	B	.	.	.	.	-1.23	*	.	.	-0.43	0.20
	Leu	1916.	A	B	.	.	.	.	-1.87	*	.	.	-0.60	0.35
10	Ala	1917.	A	B	.	.	.	.	-1.06	*	.	.	-0.30	0.21
	Ala	1918.	A	B	.	.	.	.	-0.94	.	*	.	-0.60	0.45
	Thr	1919.	A	B	.	.	.	.	-1.24	.	*	.	-0.60	0.47
	Ala	1920.	A	B	.	.	.	.	-0.70	.	.	.	-0.60	0.63
	Asn	1921.	A	B	.	.	.	.	-0.59	.	*	.	-0.60	0.90
15	Phe	1922.	A	B	.	.	.	.	-0.24	.	.	.	-0.60	0.54
	Ser	1923.	A	B	.	.	.	.	0.00	.	.	.	-0.60	0.84
	Thr	1924.	.	B	B	.	.	.	-0.29	.	.	.	-0.60	0.52
	Phe	1925.	.	B	B	.	.	.	-0.51	.	.	.	-0.60	0.59
	Tyr	1926.	.	B	B	.	.	.	-1.32	.	.	.	-0.60	0.36
20	Gly	1927.	.	B	B	.	.	.	-0.97	.	.	.	-0.60	0.21
	Met	1928.	.	B	B	.	.	.	-0.91	.	.	.	-0.60	0.24
	Leu	1929.	.	B	B	.	.	.	-1.19	.	.	.	-0.60	0.24
	Leu	1930.	.	B	B	.	.	.	-0.49	.	.	.	-0.60	0.24
	Gly	1931.	.	.	.	.	.	C	-0.83	.	.	.	-0.20	0.39
25	Tyr	1932.	A	B	.	.	.	.	-0.80	.	.	.	-0.60	0.48
	Ala	1933.	A	B	.	.	.	.	-0.20	*	*	.	-0.60	0.84
	Asn	1934.	A	B	.	.	.	.	0.72	*	*	.	-0.25	1.47
	Ala	1935.	A	B	.	.	.	.	1.19	*	.	F	0.40	1.84
	Thr	1936.	.	B	.	.	T	.	0.72	*	*	F	1.60	1.80
30	Gln	1937.	.	B	.	.	T	.	0.97	*	.	F	1.65	0.93
	Arg	1938.	.	B	.	.	T	.	0.86	*	.	F	2.00	1.53
	Gly	1939.	.	B	.	.	T	.	0.04	*	.	F	1.65	0.92
	Leu	1940.	A	B	.	.	.	.	0.63	*	.	.	0.90	0.44
	Asp	1941.	A	B	.	.	.	.	0.24	*	.	.	0.70	0.37
35	Phe	1942.	A	B	.	.	.	.	-0.57	*	.	.	-0.10	0.33
	Leu	1943.	A	B	.	.	.	.	-0.68	*	.	.	-0.60	0.33
	Asp	1944.	A	B	.	.	.	.	-0.33	*	.	.	0.30	0.33
	Phe	1945.	A	B	.	.	.	.	0.48	*	.	.	0.30	0.63
	Leu	1946.	A	B	.	.	.	.	-0.33	*	.	.	0.75	1.32
40	Asp	1947 A	A	.	.	.	.	.	0.06	*	.	F	0.75	0.65
	Asp	1948 A	A	.	.	.	.	.	0.62	.	*	F	0.65	1.09
	Glu	1949 A	.	.	B	.	.	.	0.67	.	*	F	0.70	2.06
	Leu	1950 A	.	.	B	.	.	.	1.06	.	*	.	0.90	2.47
	Thr	1951.	.	.	B	T	.	.	1.06	.	*	.	1.35	2.14
45	Tyr	1952.	.	.	B	T	.	.	0.36	.	*	.	0.50	1.02
	Lys	1953.	.	B	B	.	.	.	-0.50	.	.	F	-0.10	1.07
	Thr	1954.	.	B	B	.	.	.	-0.71	.	*	.	-0.45	0.55
	Leu	1955.	.	B	B	.	.	.	-0.76	.	*	.	-0.50	0.54
	Phe	1956.	.	B	B	.	.	.	-0.44	*	.	.	-0.55	0.20

5	Val	1957.	.	B	B	.	.	.	-0.20	*	.	.	-0.60	0.22
	Pro	1958.	.	B	.	.	.	.	-0.59	*	.	.	-0.40	0.47
	Val	1959.	.	B	.	.	.	.	-0.98	*	.	.	0.04	0.54
	Asn	1960.	.	B	.	.	T	.	-1.02	*	.	F	0.53	0.63
	Glu	1961.	.	B	.	.	T	.	-0.32	*	.	F	0.67	0.30
	Gly	1962.	.	.	.	T	T	.	0.53	.	.	F	1.81	0.68
	Phe	1963.	.	B	.	.	T	.	0.14	*	.	.	1.40	0.68
	Val	1964.	.	B	.	.	.	.	0.69	.	.	.	1.06	0.39
	Asp	1965.	.	B	.	.	.	.	-0.12	.	.	.	0.32	0.57
	Asn	1966.	.	B	.	.	.	.	-0.42	.	.	.	-0.12	0.54
	Met	1967.	.	B	.	.	.	.	-0.42	.	.	.	0.04	0.97
	Thr	1968.	.	B	.	.	.	.	0.07	*	.	.	-0.10	0.58
	Leu	1969.	.	.	.	.	.	C	0.92	*	.	F	-0.05	0.55
	Ser	1970.	.	.	.	.	.	C	0.11	.	.	F	-0.05	0.90
	Gly	1971.	.	.	.	.	T	C	0.11	.	*	F	0.15	0.51
	Pro	1972.	.	.	.	.	T	C	-0.10	.	*	F	0.60	1.08
	Asn	1973.	.	.	.	.	T	C	0.18	.	*	F	0.45	0.66
	Leu	1974.	.	B	.	.	T	.	0.40	.	*	.	0.10	0.91
	Glu	1975.	.	B	.	.	.	.	0.40	.	*	.	-0.10	0.60
	Leu	1976.	.	B	.	.	.	.	0.74	.	*	.	-0.10	0.50
	His	1977.	.	B	.	.	T	.	0.37	.	*	.	0.10	0.97
	Ala	1978.	.	B	.	.	T	.	0.06	.	*	.	0.70	0.57
	Ser	1979.	.	B	.	.	T	.	0.06	.	*	.	-0.20	0.99
	Asn	1980.	.	B	.	.	T	.	-0.76	.	.	.	-0.20	0.60
25	Ala	1981.	A	B	.	.	.	.	-0.24	.	.	.	-0.60	0.49
	Thr	1982.	A	B	.	.	.	.	-0.80	.	.	.	-0.60	0.49
	Leu	1983.	A	B	.	.	.	.	-0.21	.	.	.	-0.60	0.31
	Leu	1984.	A	B	.	.	.	.	-0.50	.	.	.	-0.60	0.49
	Ser	1985.	A	B	.	.	.	.	-0.80	.	.	.	-0.60	0.34
30	Ala	1986.	A	B	.	.	.	.	-0.21	.	.	.	-0.35	0.56
	Asn	1987.	A	B	.	.	.	.	-0.24	.	.	F	0.50	1.17
	Ala	1988.	A	.	.	.	.	C	0.61	.	*	F	0.80	0.86
	Ser	1989.	.	.	.	T	T	.	0.61	.	.	F	2.40	1.71
	Gln	1990.	.	.	.	T	T	.	0.10	.	.	F	2.50	0.88
35	Gly	1991.	.	.	.	T	T	.	0.48	.	.	F	1.65	0.72
	Lys	1992.	.	B	.	.	T	.	-0.11	.	.	F	1.00	0.83
	Leu	1993.	.	B	.	.	.	.	0.44	.	.	F	0.55	0.48
	Leu	1994.	.	B	.	.	.	.	0.44	.	.	.	0.15	0.66
	Pro	1995.	.	B	.	.	.	.	0.10	.	*	.	-0.10	0.44
40	Ala	1996.	.	B	.	.	.	.	-0.37	.	.	.	-0.40	0.53
	His	1997.	.	B	.	.	T	.	-0.71	.	*	.	-0.20	0.53
	Ser	1998.	.	.	.	.	T	C	-0.71	.	.	.	0.30	0.46
	Gly	1999.	.	B	.	.	T	.	-0.79	.	*	.	-0.20	0.38
	Leu	2000.	.	B	.	.	T	.	-1.47	*	.	.	-0.20	0.19
45	Ser	2001.	.	B	B	.	.	.	-1.18	*	.	.	-0.60	0.10
	Leu	2002.	.	B	B	.	.	.	-1.14	*	.	.	-0.60	0.14
	Ile	2003.	.	B	B	.	.	.	-1.43	*	.	.	-0.60	0.28
	Ile	2004.	.	B	B	.	.	.	-1.43	*	.	.	0.00	0.21
	Ser	2005.	.	B	B	.	.	.	-0.83	*	.	.	0.30	0.25

5	Asp	2006.	.	B	.	.	.	.	-0.53	.	.	F	0.95	0.56
	Ala	2007.	.	B	.	.	.	.	0.28	.	.	F	2.30	1.32
	Gly	2008.	.	.	.	.	T	C	0.87	.	.	F	3.00	1.59
	Pro	2009.	.	.	.	.	T	C	1.46	*	.	F	2.70	1.28
	Asp	2010.	.	.	.	T	T	.	1.47	.	.	F	2.30	1.69
	Asn	2011.	.	.	.	T	T	.	0.88	.	.	F	2.00	1.80
	Ser	2012.	.	.	.	T	.	.	1.26	.	.	F	0.90	1.17
	Ser	2013.	.	.	.	T	.	.	0.74	.	.	F	0.60	1.09
	Trp	2014.	.	B	.	.	.	.	0.37	.	.	.	-0.40	0.50
	Ala	2015.	.	B	.	.	.	.	0.16	.	.	.	-0.40	0.38
10	Pro	2016.	.	B	.	.	.	.	-0.19	.	.	.	-0.40	0.44
	Val	2017.	.	B	.	.	.	.	-0.20	.	.	.	-0.40	0.41
	Ala	2018.	.	B	.	.	T	.	-0.76	.	.	.	-0.20	0.59
	Pro	2019.	.	B	.	.	T	.	-1.32	.	.	F	-0.05	0.28
	Gly	2020.	.	B	.	.	T	.	-1.59	.	.	F	-0.05	0.28
15	Thr	2021.	.	B	.	.	T	.	-1.68	*	.	F	-0.05	0.21
	Val	2022.	.	B	B	.	.	.	-0.71	*	.	.	-0.60	0.18
	Val	2023.	.	B	B	.	.	.	-1.01	*	.	.	-0.30	0.36
	Val	2024.	.	B	B	.	.	.	-1.69	*	.	.	-0.60	0.17
	Ser	2025.	.	B	B	.	.	.	-2.20	*	.	.	-0.60	0.16
20	Arg	2026.	.	B	B	.	.	.	-2.18	.	.	.	-0.60	0.16
	Ile	2027.	.	B	B	.	.	.	-1.32	.	.	.	-0.60	0.23
	Ile	2028.	.	B	B	.	.	.	-1.36	.	.	.	-0.30	0.29
	Val	2029.	.	B	B	.	.	.	-1.10	*	.	.	-0.60	0.10
	Trp	2030.	.	B	B	.	.	.	-1.39	*	.	.	-0.60	0.15
25	Asp	2031.	.	B	B	.	.	.	-2.20	*	.	.	-0.60	0.21
	Ile	2032.	.	B	B	.	.	.	-1.31	.	.	.	-0.60	0.24
	Met	2033.	.	B	B	.	.	.	-0.77	.	.	.	-0.60	0.37
	Ala	2034.	.	.	B	.	.	C	-0.80	.	.	.	-0.40	0.22
	Phe	2035.	.	.	B	T	.	.	-1.40	.	.	.	-0.20	0.22
30	Asn	2036.	.	.	B	.	.	C	-1.43	.	*	.	-0.40	0.16
	Gly	2037.	.	B	B	.	.	.	-1.13	*	.	.	-0.60	0.21
	Ile	2038.	.	B	B	.	.	.	-1.34	*	*	.	-0.60	0.25
	Ile	2039.	.	B	B	.	.	.	-1.34	*	.	.	-0.60	0.13
	His	2040.	.	B	B	.	.	.	-0.94	*	*	.	-0.60	0.13
35	Ala	2041.	.	B	B	.	.	.	-1.16	*	.	.	-0.60	0.25
	Leu	2042.	.	B	B	.	.	.	-1.62	*	.	.	-0.60	0.54
	Ala	2043.	.	B	B	.	.	.	-1.54	*	.	.	-0.60	0.33
	Ser	2044.	.	B	.	.	T	.	-1.24	.	.	.	-0.20	0.27
	Pro	2045.	.	.	.	.	T	C	-1.42	.	.	.	0.00	0.33
40	Leu	2046.	.	.	.	T	T	.	-1.04	.	.	.	0.20	0.50
	Leu	2047.	.	B	.	.	T	.	-0.23	.	.	.	-0.20	0.58
	Ala	2048.	.	.	.	.	.	C	0.14	.	.	F	-0.05	0.65
	Pro	2049.	.	.	.	.	T	C	0.44	.	.	F	0.30	1.22
	Pro	2050.	.	.	.	.	T	C	0.07	.	.	F	0.60	2.57
45	Gln	2051.	.	.	.	.	T	C	0.02	.	.	F	0.60	2.57
	Pro	2052.	.	B	.	.	T	.	0.02	.	.	F	0.40	1.23
	Gln	2053.	A	B	.	.	.	.	0.02	.	.	F	-0.45	0.66
	Ala	2054.	A	B	.	.	.	.	-0.16	.	.	.	-0.60	0.38

5	Val	2055.	A	B	.	.	.	0.06	.	.	.	-0.60	0.32
	Leu	2056.	A	B	.	.	.	-0.53	.	.	.	-0.30	0.32
	Ala	2057.	A	B	.	.	.	-0.53	.	.	.	-0.30	0.32
	Xxx	2058.	A	B	.	.	.	-0.74	.	.	.	-0.30	0.66
	Glu	2059.	A	B	.	.	.	-1.01	.	.	F	0.60	1.24
10	Ala	2060.	A	B	.	.	.	-0.74	.	.	F	0.45	0.91
	Pro	2061.	A	B	.	.	.	-0.52	.	.	F	0.45	0.72
	Pro	2062.	.	B	.	.	.	-0.28	.	.	F	0.05	0.42
	Val	2063.	.	B	B	.	.	-0.74	.	.	.	-0.60	0.41
	Ala	2064.	.	B	B	.	.	-1.09	.	.	.	-0.60	0.20
15	Ala	2065.	.	B	B	.	.	-1.09	.	.	.	-0.60	0.13
	Gly	2066.	.	B	B	.	.	-1.73	.	.	.	-0.60	0.17
	Val	2067.	.	B	B	.	.	-2.33	.	.	.	-0.60	0.13
	Gly	2068.	A	B	.	.	.	-2.07	.	.	.	-0.60	0.10
	Ala	2069.	A	B	.	.	.	-2.07	.	.	.	-0.60	0.11
20	Val	2070.	A	B	.	.	.	-1.82	.	.	.	-0.60	0.14
	Leu	2071.	A	B	.	.	.	-2.07	.	.	.	-0.60	0.14
	Ala	2072.	A	B	.	.	.	-2.02	.	.	.	-0.60	0.14
	Ala	2073.	A	B	.	.	.	-2.49	.	.	.	-0.60	0.16
	Gly	2074.	A	B	.	.	.	-2.24	.	.	.	-0.60	0.16
25	Ala	2075.	A	B	.	.	.	-2.20	.	.	.	-0.60	0.16
	Leu	2076.	A	B	.	.	.	-2.24	.	.	.	-0.60	0.13
	Leu	2077.	A	B	.	.	.	-2.24	.	.	.	-0.60	0.10
	Gly	2078.	A	B	.	.	.	-2.00	.	.	.	-0.60	0.10
	Leu	2079.	A	B	.	.	.	-2.24	.	.	.	-0.60	0.11
30	Val	2080.	A	B	.	.	.	-2.47	.	.	.	-0.60	0.14
	Ala	2081.	A	B	.	.	.	-1.90	.	.	.	-0.60	0.12
	Gly	2082.	A	B	.	.	.	-1.90	*	.	.	-0.60	0.22
	Ala	2083.	A	B	.	.	.	-1.44	*	.	.	-0.60	0.25
	Leu	2084.	A	B	.	.	.	-1.22	*	.	.	-0.60	0.48
35	Tyr	2085.	A	B	.	.	.	-0.26	*	.	.	-0.26	0.49
	Leu	2086.	A	B	.	.	.	-0.01	*	.	.	0.38	0.95
	Arg	2087.	.	B	.	.	T	0.38	*	.	.	1.27	1.14
	Ala	2088.	.	B	.	.	T	0.76	*	F	.	2.66	1.45
	Arg	2089.	.	.	.	T	T	0.97	*	F	.	3.40	2.72
40	Gly	2090.	.	.	.	T	T	0.87	*	F	.	3.06	1.37
	Lys	2091.	.	.	.	.	C	0.98	*	F	.	2.32	1.35
	Pro	2092.	.	B	.	.	T	0.52	*	F	.	1.53	0.59
	Met	2093.	.	.	.	T	T	0.41	*	.	.	0.84	0.59
	Gly	2094.	.	B	.	.	T	0.00	*	.	.	-0.20	0.26
45	Phe	2095.	.	B	.	.	T	-0.24	*	.	.	-0.20	0.22
	Gly	2096.	.	B	.	.	.	-0.99	*	.	.	-0.40	0.23
	Phe	2097.	A	B	.	.	.	-0.78	.	.	.	-0.60	0.20
	Ser	2098.	A	.	.	.	C	-0.77	.	.	.	-0.40	0.40
	Ala	2099.	A	.	.	.	C	-0.42	.	.	.	-0.40	0.41
45	Phe	2100.	A	B	.	.	.	0.28	.	.	.	-0.30	0.81
	Gln	2101.	A	B	.	.	C	0.62	.	*	.	0.99	1.01
	Ala	2102.	A	.	.	.	C	0.73	.	*	.	1.63	1.68
	Glu	2103.	A	.	.	.	C	1.03	*	*	F	2.12	1.96

5	Asp	2104.	A	.	.	T	.	.	1.62	*	*	F	2.66	1.89
	Asp	2105.	.	.	.	T	T	.	1.93	*	*	F	3.40	3.12
	Ala	2106.	.	.	.	T	T	.	1.23	*	*	F	3.06	2.30
	Asp	2107.	.	.	.	T	T	.	1.52	*	*	F	2.72	1.19
	Asp	2108.	.	.	.	T	T	.	1.31	*	.	F	2.23	0.96
10	Xxx	2109.	.	.	.	T	.	.	1.02	*	.	F	1.54	1.47
	Phe	2110.	.	.	.	.	.	C	1.02	*	.	F	0.85	0.92
	Ser	2111.	.	.	.	.	T	C	1.61	*	.	F	0.45	0.96
	Pro	2112.	.	.	.	.	T	C	1.27	*	.	F	0.60	1.30
	Trp	2113.	.	.	.	T	T	.	0.96	*	.	F	0.80	1.48
15	Gln	2114.	.	.	.	.	T	C	1.34	*	.	F	0.81	1.60
	Glu	2115.	.	.	.	T	.	.	1.83	*	.	F	1.02	1.66
	Gly	2116.	.	.	.	T	.	.	1.82	.	.	F	1.23	2.44
	Thr	2117.	.	.	.	.	.	C	1.22	.	.	F	1.84	2.03
	Asn	2118.	.	.	.	.	T	C	0.66	.	.	F	2.10	0.97
20	Pro	2119.	.	.	.	.	T	C	0.27	.	.	F	0.99	0.73
	Thr	2120.	.	B	.	.	T	.	-0.59	.	.	F	0.58	0.64
	Leu	2121.	.	B	.	.	T	.	-0.46	.	.	.	0.22	0.30
	Val	2122.	.	B	.	.	.	.	-0.14	.	.	.	-0.19	0.30
	Xxx	2123.	.	B	.	.	.	.	-0.36	*	.	.	-0.40	0.33
25	Val	2124.	.	B	.	.	T	.	-1.00	*	.	F	-0.05	0.62
	Pro	2125.	.	B	.	.	T	.	-1.39	*	.	F	-0.05	0.62
	Asn	2126.	.	B	.	.	T	.	-0.92	*	.	F	-0.05	0.42
	Pro	2127.	.	B	.	.	T	.	-0.37	.	.	F	-0.05	0.56
	Val	2128.	.	B	.	.	.	.	0.02	.	.	F	-0.25	0.49
30	Phe	2129.	.	B	.	.	.	.	0.57	.	.	F	0.05	0.50
	Gly	2130.	.	.	.	T	T	.	0.08	.	.	F	0.65	0.47
	Ser	2131.	.	.	.	T	T	.	-0.59	.	.	F	0.35	0.55
	Asp	2132.	.	B	.	.	T	.	-0.38	.	.	F	-0.05	0.34
	Thr	2133.	.	.	.	T	T	.	0.27	.	.	F	1.25	0.60
35	Phe	2134.	.	B	.	.	.	.	0.27	*	.	.	0.50	0.69
	Cys	2135.	.	B	.	.	.	.	0.61	*	.	.	0.21	0.36
	Glu	2136.	.	B	.	.	.	.	0.91	*	.	.	0.52	0.41
	Pro	2137.	.	.	.	T	.	.	0.61	*	.	F	1.98	0.79
	Phe	2138.	.	.	.	T	.	.	0.11	*	.	F	2.74	1.99
40	Asp	2139.	.	.	.	T	T	.	0.00	*	.	F	3.10	0.95
	Asp	2140.	.	.	.	.	T	C	0.67	*	.	F	2.29	0.50
	Ser	2141.	.	.	.	.	T	C	0.67	.	.	F	2.13	1.01
	Leu	2142.	.	.	.	.	T	C	0.88	.	.	F	2.12	1.05
	Leu	2143.	A	.	.	.	.	C	0.88	.	.	F	1.41	1.05
45	Glu	2144.	A	.	.	.	.	C	0.67	.	.	F	0.99	0.68
	Glu	2145.	A	.	.	T	.	.	0.67	.	.	F	1.68	1.27
	Asp	2146.	A	.	.	T	.	.	0.66	.	.	F	2.32	2.57
	Phe	2147.	.	.	.	.	T	C	1.47	*	.	F	2.86	2.14
	Pro	2148.	.	.	.	T	T	.	2.39	*	*	F	3.40	2.14
	Asp	2149.	.	.	.	T	T	.	1.50	*	.	F	3.06	2.51
	Thr	2150 A	.	.	.	.	T	.	0.69	*	.	F	2.02	2.03
	Gln	2151 A	.	.	B	.	.	.	0.38	*	.	F	1.28	1.08
	Arg	2152.	.	B	B	.	.	.	0.22	*	.	F	0.79	0.94

	Ile	2153.	.	B	B	.	.	.	0.48	.	.	.	-0.30	0.48
	Leu	2154.	.	B	B	.	.	.	0.09	.	.	.	0.30	0.56
	Thr	2155.	.	B	B	.	.	.	0.01	.	.	.	0.30	0.36
	Val	2156.	.	B	B	.	.	.	-0.38	.	.	.	-0.30	0.66
5	Lys	2157.	.	B	B	.	.	.	-0.88	.	.	.	-0.15	1.03

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Table II:

	Res	Pos.I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
5	Met	1	.	.	B	B	.	.	.	-0.80	.	.	.	-0.60	0.21
	Val	2	.	.	B	B	.	.	.	±1.08	.	.	.	-0.60	0.24
	Thr	3	.	.	B	B	.	.	.	-1.50	.	.	.	-0.60	0.10
	Cys	4	.	.	B	B	.	.	.	-1.32	.	.	.	-0.60	0.08
	Thr	5	.	.	B	B	.	.	.	-0.93	.	.	.	-0.60	0.17
10	Cys	6	.	.	B	B	.	.	.	-0.58	.	.	.	0.04	0.20
	Leu	7	.	.	B	.	.	T	.	0.28	.	.	.	0.48	0.59
	Pro	8	.	.	B	.	.	T	.	0.24	.	*	F	1.87	0.71
	Asp	9	.	.	.	.	T	T	.	0.91	.	*	F	2.76	1.31
	Tyr	10	.	.	.	.	T	T	.	0.88	*	*	F	3.40	2.65
15	Glu	11	.	.	.	.	T	.	.	1.26	*	.	F	2.86	1.70
	Gly	12	.	.	.	.	T	T	.	1.77	*	.	F	2.42	1.07
	Asp	13	.	.	.	.	T	T	.	1.31	.	*	F	1.93	0.91
	Gly	14	.	.	.	.	T	T	.	1.42	.	*	F	1.59	0.28
	Trp	15	.	.	.	.	T	T	.	1.08	.	*	.	1.10	0.56
20	Ser	16	.	.	B	.	.	.	.	1.19	*	*	.	0.50	0.34
	Cys	17	.	.	.	.	T	.	.	1.53	*	*	.	0.90	0.67
	Arg	18	.	.	.	.	T	.	.	1.32	*	*	.	1.39	1.03
	Ala	19	.	.	.	.	T	.	.	1.00	*	*	F	2.18	1.18
	Arg	20	.	.	.	.	T	.	.	0.98	*	*	F	2.52	1.18
25	Asn	21	.	.	.	.	.	T	C	1.28	*	*	F	2.71	0.87
	Pro	22	.	.	.	.	T	T	.	1.60	*	*	F	3.40	1.44
	Cys	23	.	.	.	.	T	T	.	1.46	*	*	F	2.91	0.73
	Thr	24	.	.	.	.	T	T	.	2.16	*	*	F	2.58	0.62
	Asp	25	.	.	.	.	T	.	.	1.70	*	.	F	2.65	0.78
30	Gly	26	.	.	.	.	T	.	.	1.36	*	.	F	2.77	1.44
	His	27	.	.	.	.	T	T	.	0.90	*	.	F	2.79	0.99
	Arg	28	.	.	.	.	T	T	.	1.27	*	.	F	3.10	0.32
	Gly	29	.	.	.	.	T	T	.	1.58	*	.	F	2.49	0.43
	Gly	30	.	.	.	.	T	T	.	1.54	*	.	F	2.48	0.55
35	Cys	31	.	.	.	.	T	.	.	1.30	.	*	F	1.97	0.38
	Ser	32	.	.	B	.	.	.	.	1.33	.	*	F	0.96	0.39
	Glu	33	.	.	B	.	.	.	.	0.56	*	*	.	0.50	0.63
	His	34	.	.	B	.	.	T	.	0.09	.	.	.	0.70	0.63
	Ala	35	.	.	B	.	.	T	.	0.13	*	.	.	0.10	0.39
40	Asn	36	.	.	B	.	.	T	.	0.49	*	.	.	0.10	0.30
	Cys	37	.	.	B	.	.	T	.	0.44	*	.	.	-0.20	0.32
	Leu	38	.	.	B	.	.	.	.	-0.37	*	.	.	-0.40	0.31
	Ser	39	.	.	.	.	T	T	.	-0.33	*	.	F	0.69	0.16
	Thr	40	.	.	.	.	T	T	.	-0.06	.	*	F	1.03	0.48
45	Gly	41	.	.	.	.	T	T	.	0.06	*	.	F	1.37	0.84
	Leu	42	.	.	.	.	T	T	.	0.83	.	*	F	2.76	1.23
	Asn	43	.	.	.	.	T	T	.	0.98	.	*	F	3.40	1.67
	Thr	44	.	.	.	.	T	T	.	1.28	.	.	F	2.61	0.90
	Arg	45	.	.	.	.	T	T	.	0.92	.	.	F	2.72	1.89

5	Arg	46	.	.	B	.	.	T	.	1.23	.	*	F	1.83	0.63
	Cys	47	.	.	B	.	.	.	.	1.46	.	.	.	1.14	0.60
	Glu	48	.	.	B	.	.	.	.	1.11	*	.	.	0.80	0.31
	Cys	49	.	.	B	.	.	.	.	1.18	*	.	.	0.50	0.16
	His	50	.	.	B	.	.	T	.	0.21	*	.	.	0.10	0.45
10	Ala	51	.	.	B	.	.	T	.	-0.24	*	*	.	0.10	0.19
	Gly	52	.	.	.	.	T	T	.	0.42	.	.	.	0.20	0.36
	Tyr	53	.	.	.	.	T	T	.	0.08	*	.	.	0.50	0.44
	Val	54	.	.	.	.	T	.	.	-0.07	*	.	.	0.30	0.43
	Gly	55	.	.	.	.	T	T	.	-0.03	*	.	.	0.50	0.36
15	Asp	56	.	.	.	.	T	T	.	-0.11	*	.	.	0.50	0.40
	Gly	57	.	.	B	.	.	T	.	-0.58	*	.	.	0.10	0.29
	Leu	58	.	.	B	.	.	T	.	-0.33	*	.	.	0.10	0.24
	Gln	59	.	A	B	.	.	.	.	0.52	*	.	.	0.30	0.25
	Cys	60	.	A	B	.	.	.	.	0.57	*	.	.	0.60	0.43
20	Leu	61	.	A	B	.	.	.	.	0.57	*	.	.	0.90	0.71
	Glu	62	.	A	B	.	.	.	.	0.70	*	.	F	1.65	0.71
	Glu	63	.	A	.	.	T	.	.	1.30	*	.	F	2.50	2.03
	Ser	64	.	.	.	.	T	.	.	0.44	*	.	F	3.00	3.82
	Glu	65	.	.	.	.	.	.	C	1.11	*	.	F	2.50	1.64
25	Pro	66	.	.	.	.	.	.	C	2.03	*	.	F	2.20	1.58
	Pro	67	.	.	.	.	T	.	.	1.37	*	.	F	2.10	2.30
	Val	68	.	.	.	.	T	.	.	0.56	*	.	F	1.65	0.71
	Asp	69	.	.	B	.	.	.	.	0.51	*	.	F	0.65	0.38
	Arg	70	.	.	B	.	.	.	.	0.51	*	.	F	0.65	0.24
30	Cys	71	.	.	B	.	.	.	.	0.51	*	.	.	0.50	0.57
	Leu	72	.	.	.	.	T	.	.	0.51	*	.	F	1.05	0.53
	Gly	73	.	.	.	.	T	.	.	1.16	*	.	F	1.05	0.42
	Gln	74	.	.	.	.	.	.	C	0.49	*	.	F	0.62	1.20
	Pro	75	.	.	.	.	.	T	C	0.34	*	*	F	0.89	0.78
35	Pro	76	.	.	.	.	.	T	C	0.71	.	.	F	1.26	1.07
	Pro	77	.	.	.	.	T	T	.	1.52	.	.	F	1.53	0.83
	Cys	78	.	.	.	.	T	T	.	1.28	.	.	.	2.20	0.89
	His	79	.	.	.	.	T	T	.	0.68	.	.	.	1.98	0.58
	Ser	80	.	.	B	.	.	T	.	0.22	.	.	.	1.36	0.37
40	Asp	81	A	.	.	.	.	T	.	0.12	.	.	.	0.54	0.37
	Ala	82	A	.	.	.	.	T	.	0.33	.	.	.	0.32	0.40
	Met	83	A	.	.	.	.	.	.	0.19	.	.	.	0.50	0.49
	Cys	84	A	.	.	.	.	T	.	0.19	.	*	.	0.70	0.24
	Thr	85	A	.	.	.	.	T	.	-0.21	.	*	.	0.10	0.33
45	Asp	86	A	.	.	.	.	T	.	-0.21	.	*	.	-0.20	0.29
	Leu	87	A	.	.	.	.	T	.	0.38	.	*	.	-0.20	0.93
	His	88	A	A	.	.	.	.	.	1.02	*	*	.	0.45	1.12
	Phe	89	A	A	.	.	.	.	.	1.80	*	*	.	0.75	1.34
	Gln	90	A	A	.	.	.	.	.	1.52	*	*	F	0.90	3.17
	Glu	91	A	A	.	.	.	.	.	1.18	.	*	F	0.90	2.36
	Lys	92	A	A	.	.	.	.	.	1.13	.	.	F	0.90	2.69
	Arg	93	A	A	.	.	.	.	.	0.47	.	.	F	0.90	1.15
	Ala	94	A	A	.	.	.	.	.	1.13	.	.	F	0.75	0.58

5	Gly	95	A	A	.	.	.	.	0.32	.	.	0.30	0.39
	Val	96	A	A	.	.	.	.	0.32	*	.	-0.60	0.17
	Phe	97	.	A	B	.	.	.	-0.31	*	.	-0.60	0.28
	His	98	.	A	B	.	.	.	-0.73	*	.	-0.60	0.29
	Leu	99	.	A	B	.	.	.	-0.44	.	.	-0.60	0.56
	Gln	100	.	A	B	.	.	.	-0.44	.	.	-0.60	0.87
10	Ala	101	.	A	.	.	T	C	0.20	.	F	0.25	0.63
	Thr	102	.	A	.	.	T	.	0.66	.	F	0.40	1.19
	Ser	103	.	A	.	.	.	C	0.34	.	F	0.20	1.07
	Gly	104	.	.	.	.	.	T	0.34	.	F	0.30	1.05
	Pro	105	.	.	.	.	T	T	0.34	.	F	0.35	0.60
	Tyr	106	.	.	.	.	T	.	0.23	.	F	0.35	0.72
15	Gly	107	.	.	.	.	.	T	0.24	.	.	0.00	0.63
	Leu	108	.	.	.	.	.	C	0.54	.	.	-0.20	0.55
	Asn	109	.	A	B	.	.	.	0.30	.	.	-0.60	0.60
	Phe	110	.	A	B	.	.	.	0.51	.	.	-0.30	0.62
	Ser	111	A	A	.	.	.	.	0.17	.	.	0.45	1.30
	Glu	112	A	A	.	.	.	.	-0.08	.	F	0.45	0.81
20	Ala	113	A	A	.	.	.	.	0.07	*	.	0.30	0.95
	Glu	114	A	A	.	.	.	.	0.07	*	.	0.60	0.38
	Ala	115	A	A	.	.	.	.	0.18	.	.	0.60	0.38
	Ala	116	A	A	.	.	.	.	0.48	*	.	0.30	0.38
	Cys	117	A	A	.	.	.	.	0.13	*	.	0.60	0.38
	Glu	118	A	A	.	.	.	.	0.13	*	.	0.30	0.37
25	Ala	119	A	A	.	.	.	.	-0.72	*	.	0.30	0.37
	Gln	120	A	A	.	.	.	.	-0.94	*	.	-0.30	0.52
	Gly	121	A	A	.	.	.	.	-0.94	*	.	-0.30	0.25
	Ala	122	A	A	.	.	.	.	-0.58	*	.	-0.60	0.25
	Val	123	A	A	.	.	.	.	-1.28	*	.	-0.60	0.19
	Leu	124	.	A	B	.	.	.	-0.90	*	.	-0.60	0.17
30	Ala	125	.	A	B	.	.	.	-0.90	.	.	-0.60	0.25
	Ser	126	.	A	B	.	.	.	-1.37	*	.	-0.60	0.59
	Phe	127	.	.	B	.	.	.	-1.08	.	.	-0.40	0.59
	Pro	128	A	.	.	.	.	.	-0.81	*	.	-0.40	0.79
	Gln	129	A	A	.	.	.	.	-0.59	.	.	-0.60	0.59
	Leu	130	A	A	.	.	.	.	0.00	.	.	-0.60	0.69
35	Ser	131	A	A	.	.	.	.	0.30	.	.	-0.30	0.78
	Ala	132	A	A	.	.	.	.	0.19	.	.	-0.30	0.78
	Ala	133	A	A	.	.	.	.	0.06	*	.	-0.60	0.78
	Gln	134	A	A	.	.	.	.	-0.64	*	.	-0.30	0.57
	Gln	135	A	A	.	.	.	.	0.13	*	*	-0.60	0.49
	Leu	136	A	A	.	.	.	.	-0.38	*	*	-0.60	0.66
40	Gly	137	.	A	B	.	.	.	-0.46	.	.	-0.60	0.31
	Phe	138	.	A	B	.	.	.	-0.68	.	*	-0.60	0.10
	His	139	.	A	B	.	.	.	-1.28	*	.	-0.60	0.10
	Leu	140	.	A	B	.	.	.	-1.62	*	.	-0.60	0.10
	Cys	141	.	A	B	.	.	.	-1.10	*	.	-0.60	0.11
	Leu	142	.	A	B	.	.	.	-1.57	*	.	-0.60	0.09
45	Met	143	.	A	B	.	.	.	-1.46	*	.	-0.60	0.09

	Gly	144	A	A	.	.	.	.	.	-1.42	.	.	.	-0.60	0.16
	Trp	145	A	A	.	.	.	.	.	-0.96	.	.	.	-0.60	0.32
	Leu	146	A	A	.	.	.	.	.	-0.59	.	.	.	-0.60	0.32
	Ala	147	.	A	.	.	.	.	C	-0.09	.	.	.	-0.40	0.43
5	Asn	148	.	.	.	.	.	T	C	-0.08	.	.	F	0.15	0.59
	Gly	149	.	.	.	.	T	T	.	0.23	.	.	F	0.65	0.72
	Ser	150	.	.	.	.	.	T	C	0.31	.	.	F	0.45	0.97
	Thr	151	.	.	.	.	.	T	C	0.27	.	.	F	0.45	0.93
	Ala	152	.	.	.	.	.	.	C	0.00	.	.	F	0.25	0.70
10	His	153	.	.	B	B	.	.	.	-0.70	.	.	.	-0.60	0.39
	Pro	154	.	.	B	B	.	.	.	-0.57	*	.	.	-0.60	0.23
	Val	155	.	.	B	B	.	.	.	-1.12	.	.	.	-0.60	0.36
	Val	156	.	.	B	B	.	.	.	-1.40	*	.	.	-0.60	0.19
	Phe	157	.	.	B	B	.	.	.	-0.81	*	.	.	-0.60	0.13
15	Pro	158	.	.	B	B	.	.	.	-1.44	*	.	.	-0.60	0.29
	Val	159	.	.	B	B	.	.	.	-1.58	*	.	.	-0.29	0.21
	Ala	160	.	.	B	B	.	.	.	-0.72	*	.	.	0.32	0.24
	Asp	161	.	.	.	B	T	.	.	-0.21	.	*	.	1.63	0.24
20	Cys	162	.	.	.	.	T	T	.	0.60	*	*	.	2.34	0.33
	Gly	163	.	.	.	.	T	T	.	-0.04	.	*	F	3.10	0.63
	Asn	164	.	.	.	.	T	T	.	0.47	.	*	F	2.79	0.28
	Gly	165	.	.	.	.	T	T	.	0.17	.	*	F	2.18	0.52
	Arg	166	.	.	B	B	.	.	.	-0.69	.	*	F	0.47	0.37
25	Val	167	.	.	B	B	.	.	.	-0.32	.	*	.	0.01	0.17
	Gly	168	.	.	B	B	.	.	.	-0.79	.	*	.	-0.30	0.23
	Ile	169	.	.	B	B	.	.	.	-1.13	.	*	.	-0.60	0.10
	Val	170	.	.	B	B	.	.	.	-1.38	.	*	.	-0.60	0.13
	Ser	171	.	.	B	.	.	.	.	-1.38	.	*	.	-0.40	0.13
30	Leu	172	.	.	B	.	.	.	.	-0.48	*	*	.	-0.10	0.37
	Gly	173	.	.	B	.	.	.	.	-0.13	.	*	.	0.50	0.99
	Ala	174	A	.	.	.	.	.	.	-0.06	*	*	F	1.10	1.19
	Arg	175	.	.	.	.	.	.	C	0.50	*	*	F	1.00	1.19
	Lys	176	.	.	.	.	.	.	C	0.80	.	*	F	1.30	1.61
35	Asn	177	.	.	.	.	.	.	C	1.72	.	*	F	1.60	2.76
	Leu	178	.	.	.	.	.	.	C	1.78	.	*	F	1.90	2.76
	Ser	179	.	.	B	.	.	.	.	2.37	*	*	F	2.00	1.45
	Glu	180	A	.	.	.	.	.	.	1.67	.	*	F	2.30	1.51
	Arg	181	.	.	.	.	T	.	.	1.38	*	*	F	3.00	1.85
40	Trp	182	A	.	.	.	.	.	.	0.71	*	*	.	1.85	2.16
	Asp	183	A	.	.	.	.	T	.	0.82	*	*	.	1.60	0.67
	Ala	184	A	.	.	.	.	T	.	1.23	*	*	.	0.40	0.30
	Tyr	185	A	.	.	.	.	T	.	0.38	*	*	.	0.10	0.55
	Cys	186	.	.	B	.	.	T	.	0.27	*	*	.	0.10	0.24
45	Phe	187	.	.	B	B	.	.	.	0.56	*	*	.	-0.60	0.42
	Arg	188	.	.	B	B	.	.	.	-0.30	*	*	.	-0.30	0.45
	Val	189	.	.	B	B	.	.	.	-0.30	*	*	.	-0.30	0.62
	Gln	190	.	.	B	B	.	.	.	-0.72	*	*	.	0.30	0.72
	Asp	191	.	.	B	B	.	.	.	0.06	*	*	.	0.30	0.20
	Val	192	.	.	B	B	.	.	.	0.09	*	*	.	0.30	0.52

5	Ala	193	.	.	B	B	.	.	.	0.09	*	*	.	0.55	0.16
	Cys	194	.	.	B	B	.	.	.	0.94	*	*	.	1.10	0.19
	Arg	195	.	.	B	B	.	.	.	0.60	*	*	.	1.05	0.41
	Cys	196	.	.	B	.	.	T	.	-0.10	*	*	.	2.00	0.40
	Arg	197	.	.	.	.	T	T	.	-0.10	*	*	F	2.50	0.65
10	Asn	198	.	.	.	.	T	T	.	0.14	.	*	F	2.25	0.25
	Gly	199	.	.	.	.	T	T	.	0.81	.	*	F	1.40	0.45
	Phe	200	.	.	B	.	.	.	.	0.36	.	*	.	1.00	0.39
	Val	201	.	.	B	.	.	T	.	0.13	.	*	.	0.35	0.24
	Gly	202	.	.	.	.	T	T	.	-0.28	.	.	F	0.50	0.17
15	Asp	203	.	.	B	.	.	T	.	-0.59	*	.	F	0.25	0.26
	Gly	204	.	.	B	.	.	T	.	-0.91	*	.	F	0.25	0.51
	Ile	205	.	.	B	B	.	.	.	-0.21	*	.	F	0.45	0.28
	Ser	206	.	.	B	B	.	.	.	0.30	*	*	F	0.45	0.27
	Thr	207	.	.	B	B	.	.	.	0.69	*	*	F	0.02	0.27
20	Cys	208	.	.	B	.	.	T	.	-0.12	*	*	F	1.19	0.76
	Asn	209	.	.	.	.	T	T	.	-0.59	*	.	F	1.76	0.47
	Gly	210	.	.	.	.	T	T	.	0.30	*	.	F	1.33	0.27
	Lys	211	.	.	B	.	.	T	.	-0.26	*	.	F	1.70	0.83
	Leu	212	.	A	B	.	.	.	.	-0.76	*	*	F	1.13	0.38
25	Leu	213	.	A	B	.	.	.	.	-0.68	*	.	.	0.21	0.32
	Asp	214	.	A	B	.	.	.	.	-1.27	*	.	.	0.04	0.16
	Val	215	.	A	B	.	.	.	.	-1.23	*	.	.	-0.43	0.20
	Leu	216	A	A	.	.	.	.	.	-1.87	*	.	.	-0.60	0.35
	Ala	217	A	A	.	.	.	.	.	-1.06	*	.	.	-0.30	0.21
30	Ala	218	A	A	.	.	.	.	.	-0.94	.	*	.	-0.60	0.45
	Thr	219	A	A	.	.	.	.	.	-1.24	*	*	.	-0.60	0.47
	Ala	220	A	A	.	.	.	.	.	-0.70	.	.	.	-0.60	0.63
	Asn	221	A	A	.	.	.	.	.	-0.59	.	*	.	-0.60	0.90
	Phe	222	.	A	B	.	.	.	.	-0.24	.	.	.	-0.60	0.54
35	Ser	223	.	A	B	.	.	.	.	0.00	.	*	.	-0.60	0.84
	Thr	224	.	.	B	B	.	.	.	-0.29	.	.	.	-0.60	0.52
	Phe	225	.	.	B	B	.	.	.	-0.51	.	.	.	-0.60	0.59
	Tyr	226	.	.	B	B	.	.	.	-1.32	.	.	.	-0.60	0.36
	Gly	227	.	.	B	B	.	.	.	-0.97	.	.	.	-0.60	0.21
40	Met	228	.	.	B	B	.	.	.	-0.91	.	.	.	-0.60	0.24
	Leu	229	.	.	B	B	.	.	.	-1.19	.	.	.	-0.60	0.24
	Leu	230	.	.	B	B	.	.	.	-0.49	.	.	.	-0.60	0.24
	Gly	231	.	.	.	.	.	.	C	-0.83	.	.	.	-0.20	0.39
	Tyr	232	.	A	B	.	.	.	.	-0.80	.	.	.	-0.60	0.48
45	Ala	233	A	A	.	.	.	.	.	-0.20	*	*	.	-0.60	0.84
	Asn	234	.	A	B	.	.	.	.	0.72	*	*	.	-0.19	1.47
	Ala	235	.	A	B	.	.	.	.	1.19	*	*	F	0.52	1.84
	Thr	236	.	.	B	.	.	T	.	0.72	*	*	F	1.78	1.80
	Gln	237	.	.	B	.	.	T	.	0.97	*	*	F	1.89	0.93
	Arg	238	.	.	B	.	.	T	.	0.86	*	*	F	2.60	1.53
	Gly	239	.	.	B	.	.	T	.	0.04	*	.	F	1.89	0.92
	Leu	240	.	A	B	.	.	.	.	0.63	*	.	.	1.08	0.44
	Asp	241	.	A	B	.	.	.	.	0.24	*	.	.	0.82	0.37

	Phe	242	.	A	B	.	.	.	.	-0.57	*	.	.	-0.04	0.33
	Leu	243	.	A	B	.	.	.	.	-0.68	*	.	.	-0.60	0.33
	Asp	244	.	A	B	.	.	.	.	-0.33	*	.	.	0.30	0.33
5	Phe	245	A	A	.	.	.	.	.	0.48	*	.	.	0.30	0.63
	Leu	246	A	A	.	.	.	.	.	-0.33	*	.	.	0.75	1.32
	Asp	247	A	A	.	.	.	.	.	0.06	*	.	F	0.75	0.65
	Asp	248	A	A	.	.	.	.	.	0.62	.	*	F	0.60	1.09
	Glu	249	A	.	.	B	.	.	.	0.67	.	*	F	0.60	2.06
10	Leu	250	A	.	.	B	.	.	.	1.06	.	*	.	0.75	2.47
	Thr	251	A	.	.	B	.	.	.	1.06	.	*	.	0.75	2.14
	Tyr	252	A	.	.	B	.	.	.	0.36	.	*	.	-0.15	1.02
	Lys	253	A	.	.	B	.	.	.	-0.50	.	.	F	-0.30	1.07
	Thr	254	.	.	B	B	.	.	.	-0.71	.	*	.	-0.60	0.55
15	Leu	255	.	.	B	B	.	.	.	-0.76	.	*	.	-0.60	0.54
	Phe	256	.	.	B	B	.	.	.	-0.44	*	.	.	-0.60	0.20
	Val	257	.	.	B	B	.	.	.	-0.20	*	.	.	-0.60	0.22
	Pro	258	.	.	B	.	.	.	.	-0.59	*	.	.	-0.40	0.47
	Val	259	.	.	B	.	.	.	.	-0.98	*	.	.	-0.10	0.54
20	Asn	260	.	.	B	.	.	T	.	-1.02	*	.	F	0.25	0.63
	Glu	261	A	.	.	.	.	T	.	-0.32	*	.	F	0.25	0.30
	Gly	262	A	.	.	.	.	T	.	0.53	*	.	F	0.85	0.68
	Phe	263	A	.	.	.	.	T	.	0.14	*	.	.	0.70	0.68
	Val	264	A	.	.	.	.	.	.	0.69	*	.	.	0.50	0.39
25	Asp	265	.	.	B	.	.	.	.	-0.12	.	.	.	-0.10	0.57
	Asn	266	.	.	B	.	.	.	.	-0.42	.	.	.	-0.40	0.54
	Met	267	.	.	B	.	.	.	.	-0.42	.	.	.	-0.10	0.97
	Thr	268	.	.	B	.	.	.	.	0.07	*	.	.	0.50	0.58
	Leu	269	.	.	.	.	.	.	C	0.92	*	.	F	-0.05	0.55
30	Ser	270	.	.	.	.	.	.	C	0.11	.	.	F	-0.05	0.90
	Gly	271	.	.	.	.	.	T	C	0.11	.	*	F	0.15	0.51
	Pro	272	.	.	.	.	.	T	C	-0.10	.	*	F	0.60	1.08
	Asn	273	A	.	.	.	.	T	.	0.18	.	*	F	0.25	0.66
	Leu	274	A	.	.	.	.	T	.	0.40	.	*	.	0.10	0.91
35	Glu	275	A	.	.	.	.	.	.	0.40	.	*	.	-0.10	0.60
	Leu	276	A	.	.	.	.	.	.	0.74	.	*	.	-0.10	0.50
	His	277	A	.	.	.	.	T	.	0.37	.	*	.	0.10	0.97
	Ala	278	A	.	.	.	.	T	.	0.06	.	*	.	0.70	0.57
	Ser	279	A	.	.	.	.	T	.	0.06	.	*	.	-0.20	0.99
40	Asn	280	A	.	.	.	.	T	.	-0.76	.	.	.	-0.20	0.60
	Ala	281	A	A	.	.	.	.	.	-0.24	.	.	.	-0.60	0.49
	Thr	282	A	A	.	.	.	.	.	-0.80	.	.	.	-0.60	0.49
	Leu	283	A	A	.	.	.	.	.	-0.21	.	.	.	-0.60	0.31
	Leu	284	A	A	.	.	.	.	.	-0.50	.	.	.	-0.60	0.49
45	Ser	285	A	A	.	.	.	.	.	-0.80	.	.	.	-0.60	0.34
	Ala	286	A	A	.	.	.	.	.	-0.21	.	.	.	-0.60	0.56
	Asn	287	A	A	.	.	.	.	.	-0.24	.	.	F	0.00	1.17
	Ala	288	A	A	.	.	.	.	.	0.61	.	*	F	0.45	0.86
	Ser	289	A	.	.	.	.	T	.	0.61	.	*	F	1.00	1.71
	Gln	290	A	.	.	.	.	T	.	0.10	.	.	F	0.85	0.88

	Gly	291	.	.	.	.	T	T	.	0.48	.	.	F	0.65	0.72
	Lys	292	.	.	B	.	.	T	.	-0.11	.	.	F	0.25	0.83
	Leu	293	.	.	B	.	.	.	.	0.44	.	.	F	0.05	0.48
5	Leu	294	.	.	B	.	.	.	.	0.44	.	*	.	-0.10	0.66
	Pro	295	.	.	B	.	.	.	.	0.10	.	*	.	-0.10	0.44
	Ala	296	.	.	B	.	.	.	.	-0.37	.	.	.	-0.40	0.53
	His	297	A	.	.	.	.	T	.	-0.71	.	*	.	-0.20	0.53
	Ser	298	A	.	.	.	.	T	.	-0.71	*	.	.	0.10	0.46
	Gly	299	A	.	.	.	.	T	.	-0.79	.	*	.	-0.20	0.38
10	Leu	300	.	.	B	.	.	T	.	-1.47	*	*	.	-0.20	0.19
	Ser	301	.	.	B	B	.	.	.	-1.18	*	.	.	-0.60	0.10
	Leu	302	.	.	B	B	.	.	.	-1.14	*	.	.	-0.60	0.14
	Ile	303	.	.	B	B	.	.	.	-1.43	*	.	.	-0.60	0.28
	Ile	304	.	.	B	B	.	.	.	-1.43	*	.	.	0.00	0.21
15	Ser	305	.	.	B	B	.	.	.	-0.83	*	.	.	0.30	0.25
	Asp	306	.	.	B	.	.	.	.	-0.53	.	.	F	0.95	0.56
	Ala	307	.	.	B	.	.	.	.	0.28	.	.	F	2.30	1.32
	Gly	308	.	.	.	.	.	T	C	0.87	*	.	F	3.00	1.59
	Pro	309	.	.	.	.	.	T	C	1.46	*	.	F	2.70	1.28
20	Asp	310	.	.	.	.	T	T	.	1.47	.	.	F	2.30	1.69
	Asn	311	.	.	.	.	T	T	.	0.88	.	.	F	2.00	1.80
	Ser	312	.	.	.	.	T	.	.	1.26	.	.	F	0.90	1.17
	Ser	313	.	.	.	.	T	.	.	0.74	.	.	F	0.60	1.09
	Trp	314	.	.	B	.	.	.	.	0.37	.	.	.	-0.40	0.50
25	Ala	315	.	.	B	.	.	.	.	0.16	.	.	.	-0.40	0.38
	Pro	316	.	.	B	.	.	.	.	-0.19	.	.	.	-0.40	0.44
	Val	317	.	.	B	.	.	.	.	-0.20	.	.	.	-0.40	0.41
	Ala	318	.	.	B	.	.	T	.	-0.76	.	.	.	-0.20	0.59
	Pro	319	.	.	B	.	.	T	.	-1.32	.	.	F	-0.05	0.28
30	Gly	320	.	.	B	.	.	T	.	-1.59	.	.	F	-0.05	0.28
	Thr	321	.	.	B	.	.	T	.	-1.68	*	.	F	-0.05	0.21
	Val	322	.	.	B	B	.	.	.	-0.71	*	*	.	-0.60	0.18
	Val	323	.	.	B	B	.	.	.	-1.01	*	.	.	-0.30	0.36
	Val	324	.	.	B	B	.	.	.	-1.69	*	*	.	-0.60	0.17
35	Ser	325	.	.	B	B	.	.	.	-2.20	*	.	.	-0.60	0.16
	Arg	326	.	.	B	B	.	.	.	-2.18	.	.	.	-0.60	0.16
	Ile	327	.	.	B	B	.	.	.	-1.32	*	.	.	-0.60	0.23
	Ile	328	.	.	B	B	.	.	.	-1.36	*	.	.	-0.30	0.29
	Val	329	.	.	B	B	.	.	.	-1.10	*	.	.	-0.60	0.10
40	Trp	330	.	.	B	B	.	.	.	-1.39	*	.	.	-0.60	0.15
	Asp	331	.	.	B	B	.	.	.	-2.20	*	.	.	-0.60	0.21
	Ile	332	.	.	B	B	.	.	.	-1.31	.	.	.	-0.60	0.24
	Met	333	A	.	.	B	.	.	.	-0.77	.	.	.	-0.60	0.37
	Ala	334	A	.	.	B	.	.	.	-0.80	.	.	.	-0.60	0.22
45	Phe	335	A	.	.	B	.	.	.	-1.40	.	*	.	-0.60	0.22
	Asn	336	A	.	.	B	.	.	.	-1.43	.	*	.	-0.60	0.16
	Gly	337	A	.	.	B	.	.	.	-1.13	*	.	.	-0.60	0.21
	Ile	338	A	.	.	B	.	.	.	-1.34	*	*	.	-0.60	0.25
	Ile	339	A	.	.	B	.	.	.	-1.34	*	.	.	-0.60	0.13

5	His	340	.	.	B	B	.	.	.	-0.94	*	*	.	-0.60	0.13
	Ala	341	.	.	B	B	.	.	.	-1.16	*	.	.	-0.60	0.25
	Leu	342	.	.	B	B	.	.	.	-1.62	*	.	.	-0.60	0.54
	Ala	343	.	.	B	B	.	.	.	-1.54	*	.	.	-0.60	0.33
	Ser	344	.	.	B	.	.	T	.	-1.24	*	.	.	-0.20	0.27
10	Pro	345	.	.	.	.	.	T	C	-1.42	.	.	.	0.00	0.33
	Leu	346	.	.	.	.	T	T	.	-1.04	.	.	.	0.20	0.50
	Leu	347	.	.	B	.	.	T	.	-0.23	*	.	.	-0.20	0.58
	Ala	348	.	.	.	.	.	.	C	0.14	.	.	F	-0.05	0.65
	Pro	349	.	.	.	.	.	T	C	0.44	.	*	F	0.30	1.22
15	Pro	350	.	.	.	.	.	T	C	0.07	.	.	F	0.60	2.57
	Gln	351	.	.	.	.	.	T	C	0.02	.	*	F	0.60	2.57
	Pro	352	A	.	.	.	.	T	.	0.02	.	.	F	0.40	1.23
	Gln	353	.	A	B	.	.	.	.	0.02	.	*	F	-0.45	0.66
	Ala	354	.	A	B	.	.	.	.	-0.16	.	.	.	-0.60	0.38
20	Val	355	.	A	B	.	.	.	.	0.06	.	*	.	-0.60	0.32
	Leu	356	.	A	B	.	.	.	.	-0.53	.	*	.	-0.30	0.32
	Ala	357	.	A	B	.	.	.	.	-0.53	.	.	.	-0.30	0.32
	Xxx	358	.	A	B	.	.	.	.	-0.74	.	.	.	-0.30	0.66
	Glu	359	A	A	B	.	.	.	.	-1.01	.	.	F	0.60	1.24
25	Ala	360	.	A	B	.	.	.	.	-0.74	.	.	F	0.45	0.91
	Pro	361	A	A	.	.	.	.	.	-0.52	.	.	F	0.45	0.72
	Pro	362	A	.	.	.	.	.	.	-0.28	.	.	F	0.65	0.42
	Val	363	A	.	.	B	.	.	.	-0.74	.	.	.	-0.60	0.41
	Ala	364	A	.	.	B	.	.	.	-1.09	.	.	.	-0.60	0.20
30	Ala	365	A	.	.	B	.	.	.	-1.09	.	.	.	-0.60	0.13
	Gly	366	A	.	.	B	.	.	.	-1.73	.	.	.	-0.60	0.17
	Val	367	A	.	.	B	.	.	.	-2.33	.	.	.	-0.60	0.13
	Gly	368	.	A	B	.	.	.	.	-2.07	.	.	.	-0.60	0.10
	Ala	369	.	A	B	.	.	.	.	-2.07	.	.	.	-0.60	0.11
35	Val	370	.	A	B	.	.	.	.	-1.82	.	.	.	-0.60	0.14
	Leu	371	A	A	.	.	.	.	.	-2.07	.	.	.	-0.60	0.14
	Ala	372	A	A	.	.	.	.	.	-2.02	.	.	.	-0.60	0.14
	Ala	373	A	A	.	.	.	.	.	-2.49	.	.	.	-0.60	0.16
	Gly	374	A	A	.	.	.	.	.	-2.24	.	.	.	-0.60	0.16
40	Ala	375	A	A	.	.	.	.	.	-2.20	.	.	.	-0.60	0.16
	Leu	376	A	A	.	.	.	.	.	-2.24	.	.	.	-0.60	0.13
	Leu	377	A	A	.	.	.	.	.	-2.24	.	.	.	-0.60	0.10
	Gly	378	.	A	B	.	.	.	.	-2.00	.	.	.	-0.60	0.10
	Leu	379	.	A	B	.	.	.	.	-2.24	.	.	.	-0.60	0.11
45	Val	380	A	A	.	.	.	.	.	-2.47	.	.	.	-0.60	0.14
	Ala	381	A	A	.	.	.	.	.	-1.90	.	.	.	-0.60	0.12
	Gly	382	A	A	.	.	.	.	.	-1.90	.	*	.	-0.60	0.22
	Ala	383	A	A	.	.	.	.	.	-1.44	.	*	.	-0.60	0.25
	Leu	384	A	A	.	.	.	.	.	-1.22	.	*	.	-0.60	0.48
	Tyr	385	.	A	B	.	.	.	.	-0.26	.	*	.	-0.26	0.49
	Leu	386	.	A	B	.	.	.	.	-0.01	.	*	.	0.38	0.95
	Arg	387	.	.	B	.	.	T	.	0.38	.	*	.	1.27	1.14
	Ala	388	.	.	B	.	.	T	.	0.76	.	*	F	2.66	1.45



5	Arg	389	.	.	.	.	T	T	.	0.97	.	*	F	3.40	2.72
	Gly	390	.	.	.	.	T	T	.	0.87	.	*	F	3.06	1.37
	Lys	391	.	.	.	.	.	.	C	0.98	.	*	F	2.32	1.35
	Pro	392	.	.	B	.	.	T	.	0.52	.	*	F	1.53	0.59
	Met	393	.	.	.	.	T	T	.	0.41	.	*	.	0.84	0.59
	Gly	394	.	.	B	.	.	T	.	0.00	.	*	.	-0.20	0.26
	Phe	395	.	.	B	.	.	T	.	-0.24	*	.	.	-0.20	0.22
	Gly	396	.	.	B	.	.	.	.	-0.99	*	.	.	-0.40	0.23
10	Phe	397	.	A	B	.	.	.	.	-0.78	.	.	.	-0.60	0.20
	Ser	398	A	A	.	.	.	.	.	-0.77	.	*	.	-0.60	0.40
	Ala	399	A	A	.	.	.	.	.	-0.42	.	.	.	-0.60	0.41
	Phe	400	A	A	.	.	.	.	.	0.28	.	*	.	-0.30	0.81
15	Gln	401	A	A	.	.	.	.	.	0.62	.	*	.	0.45	1.01
	Ala	402	A	A	.	.	.	.	.	0.73	.	*	.	0.75	1.68
	Glu	403	A	A	.	.	.	.	.	1.03	*	*	F	0.90	1.96
	Asp	404	A	A	.	.	.	.	.	1.62	*	*	F	1.21	1.89
20	Asp	405	A	.	.	.	.	T	.	1.93	*	*	F	1.92	3.12
	Ala	406	A	.	.	.	.	T	.	1.23	*	*	F	2.23	2.30
	Asp	407	A	.	.	.	.	T	.	1.52	*	*	F	2.54	1.19
	Asp	408	.	.	.	.	T	T	.	1.31	*	.	F	3.10	0.96
25	Xxx	409	.	.	.	.	T	.	.	1.02	*	.	F	2.44	1.47
	Phe	410	.	.	.	.	.	.	C	1.02	*	.	F	1.78	0.92
	Ser	411	.	.	.	.	.	T	C	1.61	*	.	F	1.07	0.96
	Pro	412	.	.	.	.	.	T	C	1.27	*	.	F	0.91	1.30
30	Trp	413	.	.	.	.	T	T	.	0.96	*	.	F	0.80	1.48
	Gln	414	.	.	.	.	.	T	C	1.34	*	.	F	0.81	1.60
	Glu	415	.	.	.	.	T	.	.	1.83	*	.	F	1.02	1.66
	Gly	416	.	.	.	.	T	.	.	1.82	*	.	F	1.23	2.44
35	Thr	417	.	.	.	.	.	.	C	1.22	.	.	F	1.84	2.03
	Asn	418	.	.	.	.	.	T	C	0.66	.	.	F	2.10	0.97
	Pro	419	.	.	.	.	.	T	C	0.27	.	.	F	0.99	0.73
	Thr	420	.	.	B	.	.	T	.	-0.59	.	.	F	0.58	0.64
40	Leu	421	.	.	B	.	.	T	.	-0.46	.	.	.	0.22	0.30
	Val	422	.	.	B	.	.	.	.	-0.14	.	.	.	-0.19	0.30
	Xxx	423	.	.	B	.	.	.	.	-0.36	*	.	.	-0.40	0.33
	Val	424	.	.	B	.	.	T	.	-1.00	*	.	F	-0.05	0.62
45	Pro	425	.	.	B	.	.	T	.	-1.39	*	.	F	-0.05	0.62
	Asn	426	.	.	B	.	.	T	.	-0.92	*	.	F	-0.05	0.42
	Pro	427	.	.	B	.	.	T	.	-0.37	.	.	F	-0.05	0.56
	Val	428	.	.	B	.	.	.	.	0.02	.	.	F	-0.25	0.49
50	Phe	429	.	.	B	.	.	.	.	0.57	.	.	F	0.05	0.50
	Gly	430	.	.	.	.	T	T	.	0.08	.	.	F	0.65	0.47
	Ser	431	.	.	.	.	T	T	.	-0.59	.	.	F	0.35	0.55
	Asp	432	.	.	B	.	.	T	.	-0.38	.	.	F	-0.05	0.34
	Thr	433	.	.	.	.	T	T	.	0.27	*	.	F	1.25	0.60
	Phe	434	.	.	B	.	.	.	.	0.27	*	.	.	0.80	0.69
	Cys	435	.	.	B	.	.	.	.	0.61	*	.	.	0.50	0.36
	Glu	436	.	.	B	.	.	.	.	0.91	*	.	.	0.80	0.41
	Pro	437	.	.	.	.	T	.	.	0.61	*	.	F	2.25	0.79

5	Phe	438	.	.	.	.	T	.	.	0.11	*	.	F	3.00	1.99
	Asp	439	A	.	.	.	.	T	.	0.00	*	.	F	2.35	0.95
	Asp	440	A	.	.	.	.	T	.	0.67	*	.	F	1.75	0.50
	Ser	441	A	.	.	.	.	T	.	0.67	*	.	F	1.60	1.01
	Leu	442	A	.	.	.	.	T	.	0.88	.	*	F	1.60	1.05
10	Leu	443	A	A	.	.	.	.	.	0.88	.	*	F	0.90	1.05
	Glu	444	A	A	.	.	.	.	.	0.67	.	.	F	0.45	0.68
	Glu	445	A	A	.	.	.	.	.	0.67	.	.	F	0.60	1.27
	Asp	446	A	A	.	.	.	.	.	0.66	*	.	F	0.90	2.57
	Phe	447	A	.	.	.	.	T	.	1.47	*	*	F	1.30	2.14
15	Pro	448	A	.	.	.	.	T	.	2.39	*	*	F	1.30	2.14
	Asp	449	A	.	.	.	.	T	.	1.50	*	*	F	1.30	2.51
	Thr	450	A	.	.	.	.	T	.	0.69	*	.	F	1.00	2.03
	Gln	451	A	.	.	B	.	.	.	0.38	*	*	F	0.60	1.08
	Arg	452	A	.	.	B	.	.	.	0.22	*	.	F	0.45	0.94
20	Ile	453	.	.	B	B	.	.	.	0.48	.	.	.	-0.30	0.48
	Leu	454	.	.	B	B	.	.	.	0.09	.	.	.	0.30	0.56
	Thr	455	.	.	B	B	.	.	.	0.01	.	.	.	0.30	0.36
	Val	456	.	.	B	B	.	.	.	-0.38	.	.	.	-0.30	0.66
	Lys	457	.	.	B	B	.	.	.	-0.88	.	.	.	-0.15	1.03

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Table III:

	Res	Pos.	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
5	Met	1	A	A	.	.	.	.	.	.	-1.43	.	.	.	-0.60	0.25
	Gly	2	A	A	.	.	.	.	.	.	-1.86	.	.	.	-0.60	0.16
	Leu	3	.	A	B	.	.	.	.	.	-2.32	.	.	.	-0.60	0.10
	Leu	4	.	A	B	.	.	.	.	.	-2.14	.	.	.	-0.60	0.08
	Leu	5	.	A	B	.	.	.	.	.	-2.57	.	.	.	-0.60	0.12
10	Leu	6	.	A	B	.	.	.	.	.	-2.78	.	.	.	-0.60	0.12
	Val	7	.	A	B	.	.	.	.	.	-3.24	.	.	.	-0.60	0.12
	Pro	8	.	A	B	.	.	.	.	.	-3.24	.	.	.	-0.60	0.12
	Leu	9	.	A	B	.	.	.	.	.	-2.64	.	.	.	-0.60	0.12
	Leu	10	.	A	B	.	.	.	.	.	-2.18	.	.	.	-0.60	0.25
15	Leu	11	.	A	B	.	.	.	.	.	-1.67	.	.	.	-0.60	0.16
	Leu	12	.	.	B	.	.	.	T	.	-1.06	.	.	.	-0.20	0.26
	Pro	13	.	.	B	.	.	.	T	.	-1.19	.	F	.	-0.05	0.50
	Gly	14	.	.	.	.	.	T	T	.	-1.19	.	F	.	0.35	0.60
	Ser	15	.	.	.	.	.	T	T	.	-0.59	.	F	.	0.35	0.60
20	Tyr	16	.	.	B	.	.	.	.	.	-0.48	.	.	.	-0.40	0.60
	Gly	17	.	.	B	.	.	.	.	.	0.09	.	.	.	-0.40	0.53
	Leu	18	.	.	B	B	.	.	.	.	0.06	.	.	.	-0.60	0.62
	Pro	19	.	.	B	B	.	.	.	.	0.06	.	.	.	-0.60	0.62
	Phe	20	.	.	B	B	.	.	.	.	-0.34	.	.	.	-0.60	0.62
25	Tyr	21	.	.	B	B	.	.	.	.	-0.34	.	.	.	-0.60	0.65
	Tyr	22	.	.	B	B	.	.	.	.	-0.24	.	.	.	-0.60	0.65
	Gly	23	.	.	B	B	.	.	.	.	0.27	.	.	.	-0.45	1.18
	Phe	24	.	.	B	B	.	.	.	.	0.48	.	.	.	-0.45	1.01
	Tyr	25	.	.	B	B	.	.	.	.	0.88	.	.	.	-0.45	1.04
30	Tyr	26	.	.	.	.	.	T	T	.	0.53	.	.	.	0.65	1.41
	Ser	27	.	.	.	.	.	.	T	C	0.78	.	.	F	0.90	1.64
	Asn	28	.	.	.	.	.	T	T	.	1.12	.	.	F	1.40	1.69
	Ser	29	.	.	.	.	.	.	T	C	1.82	.	.	F	2.40	1.80
	Ala	30	.	.	.	.	.	T	.	C	2.07	.	.	F	3.00	2.32
35	Asn	31	.	.	.	.	.	.	.	C	1.50	.	.	F	2.50	2.32
	Asp	32	.	.	.	.	.	T	T	.	1.46	.	.	F	2.30	1.43
	Gln	33	.	.	B	.	.	.	T	.	1.46	.	.	F	1.60	1.40
	Asn	34	.	.	B	.	.	.	T	.	1.41	.	.	F	1.30	1.40
	Leu	35	.	.	B	.	.	.	T	.	1.97	.	.	F	1.15	0.83
40	Gly	36	.	.	.	.	.	T	.	.	1.62	*	.	F	1.05	0.65
	Asn	37	.	.	.	.	.	T	T	.	1.67	.	.	F	1.55	0.40
	Gly	38	.	.	.	.	.	.	T	C	1.67	*	.	F	2.25	0.97
	His	39	.	.	.	.	.	.	T	C	0.86	*	.	F	3.00	1.64
	Gly	40	.	.	.	.	.	.	T	C	1.28	*	.	F	2.55	0.84
45	Lys	41	.	.	B	.	.	.	.	.	1.62	*	.	F	2.00	1.09
	Asp	42	.	.	B	.	.	.	.	.	1.28	*	.	F	1.70	1.28
	Leu	43	.	.	B	.	.	.	T	.	0.77	*	.	F	1.60	1.28
	Xxx	44	.	.	B	.	.	.	T	.	0.84	*	*	F	0.85	0.48
	Asn	45	A	.	B	.	.	.	T	.	0.38	*	.	F	0.85	0.57

5	Gly	46	A	.	.	.	.	T	.	-0.52	*	.	F	0.25	0.57
	Val	47	.	.	B	B	.	.	.	-1.38	*	*	F	-0.15	0.33
	Lys	48	.	.	B	B	.	.	.	-0.57	*	*	F	-0.45	0.15
	Leu	49	.	.	B	B	.	.	.	-0.49	*	.	.	-0.30	0.27
	Val	50	.	.	B	B	.	.	.	-0.70	*	.	.	-0.30	0.52
10	Val	51	.	.	B	B	.	.	.	-0.36	*	*	.	0.30	0.40
	Glu	52	.	.	B	B	.	.	.	0.50	*	*	F	0.45	0.85
	Thr	53	A	.	.	.	.	.	.	0.14	*	.	F	1.10	1.97
	Pro	54	A	.	.	.	.	.	.	0.14	.	.	F	1.10	3.83
	Glu	55	A	.	.	.	.	.	.	0.30	*	.	F	1.10	1.83
15	Glu	56	A	.	.	B	.	.	.	0.84	*	.	F	0.60	1.10
	Thr	57	A	.	.	B	.	.	.	0.60	.	.	F	0.60	1.02
	Leu	58	A	.	.	B	.	.	.	0.91	.	.	.	-0.30	0.93
	Phe	59	A	.	.	B	.	.	.	0.78	.	.	.	-0.60	0.93
	Thr	60	A	.	.	B	.	.	.	0.19	.	.	.	-0.60	0.63
20	Tyr	61	A	.	.	.	.	T	.	-0.11	.	.	.	-0.20	0.78
	Gln	62	.	.	.	.	T	T	.	-0.66	.	.	.	0.35	1.20
	Gly	63	.	.	.	.	T	T	.	-0.73	.	.	F	0.35	0.62
	Ala	64	.	.	.	.	T	T	.	-0.84	.	.	.	0.20	0.28
	Ser	65	.	.	B	B	.	.	.	-0.74	.	.	.	-0.60	0.13
25	Val	66	.	.	B	B	.	.	.	-1.17	.	*	.	-0.60	0.21
	Ile	67	.	.	B	B	.	.	.	-1.06	.	*	.	-0.60	0.11
	Leu	68	.	.	B	.	.	T	.	-0.96	.	*	.	0.10	0.16
	Pro	69	.	.	B	.	.	T	.	-0.26	.	*	.	-0.20	0.34
	Cys	70	.	.	B	.	.	T	.	-0.20	.	*	.	0.10	0.94
30	Arg	71	.	.	B	.	.	T	.	0.66	.	*	.	0.25	1.79
	Tyr	72	.	.	B	.	.	.	.	1.33	.	*	.	0.65	2.00
	Arg	73	.	.	.	.	T	.	.	1.56	.	*	.	1.05	5.78
	Tyr	74	.	A	B	.	.	.	.	0.96	.	*	.	0.75	2.98
	Glu	75	.	A	B	.	.	.	.	0.77	.	*	.	-0.15	1.57
35	Pro	76	.	A	B	.	.	.	.	0.36	.	*	.	-0.10	0.59
	Ala	77	.	A	B	.	.	.	.	0.39	.	*	.	0.10	0.51
	Leu	78	.	A	B	.	.	.	.	0.39	*	.	.	0.30	0.45
	Val	79	.	A	B	.	.	.	.	0.74	*	.	.	0.50	0.58
	Ser	80	.	.	B	.	.	T	.	-0.11	*	.	F	2.00	1.12
40	Pro	81	.	.	B	.	.	T	.	0.21	.	*	F	1.80	1.00
	Arg	82	.	.	B	.	.	T	.	-0.06	.	*	F	1.90	2.65
	Arg	83	.	.	B	.	.	T	.	0.80	.	*	F	1.70	1.47
	Val	84	.	.	B	B	.	.	.	1.37	.	*	.	0.95	1.90
	Arg	85	.	.	B	B	.	.	.	1.38	*	*	.	0.75	1.02
45	Val	86	.	.	B	B	.	.	.	1.63	*	*	.	-0.30	0.55
	Lys	87	.	.	B	B	.	.	.	0.71	*	*	.	-0.15	1.47
	Trp	88	.	.	B	B	.	.	.	0.30	*	*	.	-0.30	0.62
	Trp	89	.	.	B	B	.	.	.	1.16	.	*	.	-0.45	1.12
	Lys	90	.	.	B	B	.	.	.	1.04	.	*	.	0.30	0.97
	Leu	91	.	.	.	.	.	C	.	1.56	*	.	F	0.70	1.48
	Ser	92	.	.	.	.	.	T	C	0.92	*	.	F	1.80	1.40
	Glu	93	.	.	.	.	.	T	C	1.00	*	.	F	2.25	0.71
	Asn	94	.	.	.	.	.	T	C	1.29	.	*	F	2.40	1.32

5	Gly	95	.	.	.	.	T	C	1.29	.	.	F	3.00	1.71
	Ala	96	.	.	.	.	.	C	2.10	.	.	F	2.50	1.97
	Pro	97	A	.	.	.	.	.	1.54	.	.	F	2.00	2.05
	Glu	98	A	.	.	.	.	.	0.73	.	.	F	1.70	1.54
	Lys	99	A	.	.	B	.	.	-0.12	.	.	F	1.20	1.25
10	Asp	100	A	.	.	B	.	.	-0.37	.	.	F	0.75	0.60
	Val	101	A	.	.	B	.	.	-0.67	.	.	.	0.60	0.35
	Leu	102	A	.	.	B	.	.	-0.80	.	.	.	-0.30	0.12
	Val	103	A	.	.	B	.	.	-1.61	.	*	.	-0.60	0.07
	Ala	104	A	.	.	B	.	.	-1.54	.	*	.	-0.60	0.08
15	Ile	105	A	.	.	B	.	.	-1.58	.	*	.	-0.60	0.19
	Gly	106	A	.	.	.	.	.	-0.61	.	*	.	-0.40	0.35
	Leu	107	.	.	B	.	.	.	-0.10	.	*	.	0.50	0.68
	Arg	108	.	.	B	.	.	.	0.06	.	*	.	0.93	1.31
	His	109	.	.	B	.	.	.	0.30	*	*	.	1.21	1.15
20	Arg	110	.	.	B	.	T	.	1.19	*	*	.	1.69	1.37
	Ser	111	.	.	.	.	T	T	1.29	.	*	F	2.82	1.17
	Phe	112	.	.	.	.	T	T	2.10	.	*	F	2.80	1.35
	Gly	113	.	.	.	.	T	T	1.64	*	*	F	2.52	1.19
	Asp	114	.	.	.	.	T	.	1.79	*	*	F	1.29	0.88
25	Tyr	115	.	.	.	.	T	T	0.82	*	*	F	1.96	1.99
	Gln	116	.	.	.	.	T	T	1.09	*	*	F	1.68	1.49
	Gly	117	.	.	B	.	.	T	0.98	*	*	F	1.00	1.22
	Arg	118	.	.	B	.	.	T	1.43	*	*	F	-0.05	0.64
	Val	119	.	.	B	B	.	.	1.43	*	*	.	0.30	0.72
30	His	120	.	.	B	B	.	.	1.68	*	*	.	0.45	1.27
	Leu	121	A	.	.	B	.	.	1.72	*	*	.	0.75	1.08
	Arg	122	A	.	.	.	.	T	2.07	*	*	F	1.30	2.91
	Gln	123	A	.	.	.	.	T	1.92	*	*	F	1.30	3.71
	Asp	124	A	.	.	.	.	T	2.78	.	*	F	1.30	6.12
35	Lys	125	A	.	.	.	.	T	1.96	.	*	F	1.30	5.22
	Glu	126	A	.	.	.	.	.	2.47	.	*	F	1.10	2.24
	His	127	A	.	.	.	.	.	1.97	.	.	F	1.10	1.79
	Asp	128	A	.	.	.	.	T	1.97	*	*	.	1.15	1.15
	Val	129	A	.	.	.	.	T	1.08	*	*	.	1.15	1.15
40	Ser	130	A	.	.	.	.	T	1.03	.	*	F	0.85	0.59
	Xxx	131	A	.	.	.	.	T	0.64	*	*	F	0.85	0.61
	Glu	132	A	A	.	.	.	.	-0.13	*	*	F	0.60	1.06
	Ile	133	A	A	.	.	.	.	-0.02	.	*	F	-0.15	0.65
	Gln	134	A	A	.	.	.	.	0.02	.	*	F	0.45	1.00
45	Xxx	135	A	A	.	.	.	.	0.32	.	.	.	0.30	0.47
	Leu	136	.	A	B	.	.	.	0.71	.	.	.	0.79	1.17
	Arg	137	.	A	B	.	.	.	0.47	.	.	.	1.43	1.13
	Leu	138	.	A	B	.	.	.	1.01	.	*	.	1.47	1.38
	Glu	139	.	A	.	.	T	.	1.12	*	*	F	2.36	1.66
	Asp	140	.	.	.	.	T	T	1.27	.	*	F	3.40	1.66
	Tyr	141	.	.	.	.	T	T	2.19	.	*	F	2.76	3.16
	Gly	142	.	.	.	.	T	T	1.41	*	*	F	2.72	3.57
	Arg	143	.	.	.	.	T	T	2.22	*	*	.	1.93	1.15

5	Tyr	144	.	.	B	.	.	.	1.37	*	*	.	0.99	1.27
	Arg	145	.	.	B	.	.	.	0.98	*	*	.	0.80	0.95
	Cys	146	.	.	B	.	.	.	1.22	*	*	.	0.80	0.62
	Glu	147	.	.	B	.	.	.	1.22	*	*	.	0.80	0.66
	Val	148	.	.	B	.	.	T	0.30	*	*	.	1.00	0.33
10	Xxx	149	.	.	B	.	.	T	0.54	*	*	.	0.70	0.51
	Asp	150	.	.	B	.	.	T	0.43	.	*	F	1.15	0.51
	Gly	151	A	.	.	.	.	T	1.10	*	.	F	1.30	1.16
	Leu	152	A	.	.	.	.	.	0.80	*	.	F	1.10	1.56
	Glu	153	A	.	.	.	.	.	1.31	*	.	F	1.10	1.26
15	Asp	154	A	.	.	.	.	T	0.89	*	.	F	1.30	1.26
	Glu	155	A	.	.	.	.	T	0.03	*	.	F	1.30	1.26
	Ser	156	A	.	.	.	.	T	0.38	.	.	F	1.15	0.54
	Gly	157	A	.	.	.	.	T	0.38	.	.	F	1.15	0.56
	Leu	158	A	A	.	.	.	.	0.38	.	*	F	0.45	0.27
20	Val	159	A	A	.	.	.	.	-0.43	.	*	.	0.30	0.34
	Glu	160	A	A	.	.	.	.	-0.32	*	*	.	-0.30	0.29
	Leu	161	A	A	.	.	.	.	-0.37	*	*	.	0.30	0.68
	Glu	162	A	A	.	.	.	.	-0.88	*	*	.	0.60	0.91
	Leu	163	A	.	.	B	.	.	-0.92	*	*	.	0.60	0.39
25	Arg	164	A	.	.	B	.	.	-0.77	*	*	.	-0.30	0.35
	Gly	165	.	.	.	B	T	.	-0.98	.	*	.	0.10	0.17
	Val	166	.	.	B	B	.	.	-0.41	.	*	.	-0.60	0.33
	Val	167	.	.	B	B	.	.	-0.41	*	*	.	-0.60	0.26
	Phe	168	.	.	B	.	.	T	0.10	*	.	.	-0.20	0.46
30	Pro	169	.	.	B	.	.	T	-0.22	*	.	.	-0.20	0.83
	Tyr	170	.	.	.	.	T	T	0.12	.	.	.	0.63	1.73
	Gln	171	.	.	.	.	.	T	0.63	.	*	F	0.86	3.21
	Ser	172	.	.	.	.	.	T	1.60	.	*	F	1.44	2.05
	Pro	173	.	.	.	.	T	T	2.06	.	*	F	2.52	2.56
35	Asn	174	.	.	.	.	T	T	2.27	.	*	F	2.80	2.32
	Gly	175	.	.	.	.	T	T	1.81	.	*	F	2.52	3.00
	Arg	176	.	.	.	.	T	.	1.81	.	*	F	1.44	1.68
	Tyr	177	.	.	B	.	.	.	1.41	.	*	.	0.61	1.68
	Gln	178	.	A	B	.	.	.	1.59	.	*	.	-0.17	1.47
40	Phe	179	.	A	B	.	.	.	1.59	.	*	.	-0.45	1.02
	Asn	180	.	A	B	.	.	.	1.59	.	*	.	-0.45	1.13
	Phe	181	.	A	.	.	.	.	1.48	*	*	.	0.10	0.64
	His	182	.	A	.	.	T	.	1.72	.	*	.	0.25	1.29
	Glu	183	.	A	.	.	T	.	0.87	.	*	F	1.00	1.39
45	Gly	184	.	A	.	.	T	.	0.90	.	.	F	0.40	1.19
	Gln	185	.	A	.	.	T	.	0.31	*	.	F	0.85	0.47
	Gln	186	A	A	.	.	.	.	1.01	*	.	F	0.45	0.27
	Val	187	A	A	.	.	.	.	1.04	.	.	.	0.30	0.48
	Cys	188	A	A	.	.	.	.	0.46	.	.	.	0.30	0.48
	Ala	189	A	A	.	.	.	.	0.21	.	.	.	-0.30	0.28
	Glu	190	A	A	.	.	.	.	-0.64	.	.	.	-0.30	0.38
	Gln	191	A	A	.	.	.	.	-1.50	.	.	.	-0.30	0.53
	Ala	192	A	A	.	.	.	.	-1.23	.	.	.	-0.30	0.39

5	Ala	193	A	A	.	.	.	.	.	-0.87	.	.	.	-0.30	0.23
	Val	194	A	A	.	.	.	.	.	-0.98	.	.	.	-0.60	0.17
	Val	195	A	A	.	.	.	.	.	-0.98	.	.	.	-0.60	0.15
	Ala	196	A	A	.	.	.	.	.	-0.98	.	.	.	-0.60	0.26
	Ser	197	A	A	.	.	.	.	.	-1.20	*	.	.	-0.30	0.60
10	Phe	198	A	A	.	.	.	.	.	-1.31	*	*	.	-0.60	0.66
	Glu	199	A	A	.	.	.	.	.	-0.34	*	*	.	-0.60	0.57
	Gln	200	A	A	.	.	.	.	.	-0.08	*	.	.	-0.30	0.83
	Leu	201	A	A	.	.	.	.	.	0.22	*	*	.	-0.30	0.97
	Phe	202	A	A	.	.	.	.	.	0.52	*	.	.	-0.30	0.59
15	Arg	203	A	A	.	.	.	.	.	1.22	*	*	.	-0.30	0.59
	Ala	204	A	A	.	.	.	.	.	0.88	*	.	.	0.45	1.24
	Trp	205	A	A	.	.	.	.	.	0.07	*	.	.	0.67	1.42
	Glu	206	A	A	.	.	.	.	.	0.88	*	.	F	0.89	0.60
	Glu	207	A	A	.	.	.	.	.	1.29	*	*	F	1.11	0.99
20	Gly	208	.	.	.	.	T	T	.	0.51	*	.	F	2.13	0.99
	Leu	209	.	.	.	.	T	T	.	1.10	*	.	.	2.20	0.30
	Asp	210	.	.	.	.	T	T	.	0.80	*	.	.	1.38	0.28
	Trp	211	.	.	.	.	T	T	.	0.46	*	.	.	0.86	0.29
	Cys	212	A	.	.	.	.	.	.	0.17	.	.	.	0.04	0.35
25	Asn	213	.	.	.	.	T	T	.	-0.30	.	.	.	0.42	0.22
	Ala	214	.	.	.	.	T	T	.	0.51	.	.	.	0.20	0.17
	Gly	215	.	.	.	.	T	T	.	0.51	.	.	.	0.20	0.55
	Trp	216	.	.	.	.	.	T	C	0.21	.	.	.	0.30	0.57
	Leu	217	.	.	.	.	.	.	C	0.57	.	.	.	-0.20	0.57
30	Gln	218	.	.	B	.	.	.	.	-0.29	.	.	F	-0.25	0.84
	Asp	219	.	.	B	.	.	.	.	0.30	.	.	F	-0.25	0.59
	Ala	220	.	.	B	B	.	.	.	0.40	.	.	F	0.00	1.24
	Thr	221	.	.	B	B	.	.	.	0.48	.	*	.	-0.15	1.12
	Val	222	.	.	B	B	.	.	.	0.40	.	.	.	-0.15	1.04
35	Gln	223	.	.	B	B	.	.	.	-0.20	.	*	.	-0.60	0.72
	Tyr	224	.	.	B	B	.	.	.	-1.01	.	*	.	-0.60	0.50
	Pro	225	.	.	B	B	.	.	.	-0.63	*	*	.	-0.60	0.55
	Ile	226	.	.	B	B	.	.	.	-0.21	*	.	.	-0.60	0.49
	Met	227	.	.	B	B	.	.	.	0.64	*	.	.	-0.60	0.61
40	Leu	228	.	.	B	B	.	.	.	0.43	*	.	.	-0.30	0.69
	Pro	229	.	.	B	B	.	.	.	0.01	.	.	F	0.25	1.52
	Arg	230	.	.	B	.	.	.	.	-0.12	.	.	F	0.55	0.82
	Gln	231	.	.	B	.	.	T	.	0.42	.	.	F	1.60	0.99
	Pro	232	.	.	.	.	T	T	.	0.81	*	.	F	2.25	0.63
45	Cys	233	.	.	.	.	T	T	.	1.62	*	.	F	2.50	0.50
	Gly	234	.	.	.	.	T	T	.	1.02	*	.	F	2.25	0.48
	Gly	235	.	.	.	.	.	T	C	0.32	*	.	F	1.80	0.26
	Pro	236	.	.	.	.	.	T	C	0.11	.	.	F	0.95	0.48
	Asp	237	.	.	B	.	.	T	.	-0.02	*	.	F	1.10	0.75
	Leu	238	.	.	B	.	.	T	.	-0.21	*	*	F	0.85	0.75
	Ala	239	.	.	B	.	.	T	.	0.24	*	*	F	0.25	0.36
	Pro	240	.	.	B	.	.	T	.	0.29	*	*	F	0.85	0.42
	Gly	241	.	.	B	.	.	T	.	0.26	*	*	F	0.25	0.69

5	Val	242	.	.	B	.	.	T	.	-0.09	*	*	F	0.40	1.07
	Arg	243	.	.	B	.	.	T	.	0.51	*	.	F	0.25	0.69
	Ser	244	.	.	B	.	.	T	.	1.21	*	.	F	0.74	1.07
	Tyr	245	.	.	B	.	.	T	.	1.39	*	*	F	1.68	2.83
	Gly	246	.	.	.	.	.	T	C	1.84	*	.	F	2.22	1.96
10	Pro	247	.	.	.	.	T	T	.	2.81	*	.	F	2.76	2.87
	Arg	248	.	.	.	.	T	T	.	1.89	*	.	F	3.40	3.59
	His	249	.	.	B	.	.	T	.	2.16	*	.	F	2.66	2.99
	Arg	250	.	.	B	.	.	T	.	2.51	*	.	F	2.54	2.63
	Arg	251	.	.	B	.	.	.	.	2.61	*	.	.	2.07	2.63
15	Leu	252	.	.	B	.	.	.	.	2.82	*	*	.	1.95	3.03
	His	253	.	.	.	.	T	T	.	1.86	*	*	.	2.43	2.58
	Arg	254	.	.	.	.	T	T	.	1.19	*	.	.	2.20	0.98
	Tyr	255	.	.	.	.	T	T	.	0.41	*	.	.	1.53	1.03
	Asp	256	.	.	B	.	.	T	.	-0.40	*	.	.	0.76	0.40
20	Val	257	.	.	B	B	.	.	.	-0.18	.	.	.	-0.16	0.18
	Phe	258	.	.	B	B	.	.	.	-0.46	.	.	.	-0.38	0.12
	Cys	259	.	.	B	B	.	.	.	-1.16	.	*	.	-0.60	0.10
	Phe	260	.	.	B	B	.	.	.	-1.72	.	.	.	-0.60	0.14
	Ala	261	A	.	.	B	.	.	.	-2.11	.	.	.	-0.60	0.13
25	Thr	262	A	.	.	B	.	.	.	-1.60	.	*	.	-0.60	0.31
	Ala	263	A	.	.	B	.	.	.	-0.79	*	*	.	-0.60	0.35
	Leu	264	A	.	.	.	.	T	.	-0.98	.	*	.	0.10	0.68
	Xxx	265	A	.	.	.	.	T	.	-0.52	.	*	F	0.25	0.35
	Gly	266	.	.	.	.	T	T	.	-0.18	.	*	F	0.35	0.54
30	Arg	267	.	.	B	.	.	T	.	-0.68	.	*	.	-0.05	1.03
	Val	268	.	.	B	B	.	.	.	-0.48	.	*	.	-0.60	0.67
	Tyr	269	.	.	B	B	.	.	.	0.30	.	*	.	-0.60	0.86
	Tyr	270	.	.	B	B	.	.	.	0.48	.	*	.	-0.60	0.60
	Leu	271	.	.	B	B	.	.	.	0.82	.	*	.	-0.45	1.25
35	Xxx	272	.	.	B	B	.	.	.	0.32	.	*	.	-0.45	1.38
	His	273	.	.	B	.	.	T	.	0.37	.	.	F	0.40	1.13
	Pro	274	.	.	.	.	.	T	C	0.30	.	.	F	0.60	1.13
	Glu	275	A	.	.	.	.	T	.	-0.27	.	.	F	1.00	1.27
	Xxx	276	A	.	.	.	.	T	.	0.23	.	.	F	0.25	0.77
40	Leu	277	A	A	.	.	.	.	.	0.23	.	.	.	-0.30	0.72
	Thr	278	A	A	.	.	.	.	.	-0.32	*	.	.	-0.30	0.53
	Leu	279	A	A	.	.	.	.	.	0.00	.	.	.	-0.60	0.42
	Thr	280	A	A	.	.	.	.	.	0.00	*	.	F	-0.15	1.00
	Xxx	281	A	A	.	.	.	.	.	-0.20	*	.	F	0.60	1.20
45	Ala	282	A	A	.	.	.	.	.	-0.06	*	.	F	0.60	1.46
	Arg	283	A	A	.	.	.	.	.	0.26	*	.	F	0.75	0.54
	Glu	284	A	A	.	.	.	.	.	1.07	*	.	.	0.60	0.74
	Ala	285	A	A	.	.	.	.	.	1.42	*	.	.	0.75	1.26
	Cys	286	A	A	.	.	.	.	.	1.42	*	.	.	0.75	1.29
50	Gln	287	A	A	.	.	.	.	.	1.62	*	.	.	0.60	0.95
	Glu	288	A	A	.	.	.	.	.	1.12	.	.	.	0.75	1.20
	Lys	289	A	A	.	.	.	.	.	0.73	.	.	.	0.75	2.87



Table IV:

	Res	Pos.	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
5	Met	1	.	.	.	B	.	.	.	.	0.13	.	*	.	0.24	0.82
	Thr	2	.	.	.	.	.	.	.	C	0.57	.	.	.	0.78	0.63
	Gly	3	.	.	.	.	.	.	T	C	0.92	.	*	.	1.92	0.99
	Pro	4	.	.	.	.	.	T	T	.	1.36	.	*	.	2.61	1.36
	Gly	5	.	.	.	.	.	T	T	.	1.08	.	*	F	3.40	1.89
	Lys	6	A	.	.	.	.	.	T	.	1.68	.	*	F	2.66	1.02
10	His	7	A	A	.	.	.	.	.	.	1.32	.	*	F	1.92	1.15
	Lys	8	A	A	.	.	.	.	.	.	1.71	.	*	F	1.60	0.62
	Cys	9	A	A	.	.	.	.	.	.	1.62	.	*	.	1.28	0.62
	Glu	10	A	A	.	.	.	.	.	.	1.93	.	*	.	1.11	0.61
	Cys	11	.	.	B	.	.	.	T	.	1.64	.	*	.	1.68	0.42
15	Lys	12	.	.	B	.	.	.	T	.	0.82	.	*	.	1.70	1.22
	Ser	13	.	.	B	.	.	.	T	.	0.43	.	*	.	1.38	0.52
	His	14	.	.	B	.	.	.	T	.	1.10	.	*	.	0.61	0.96
	Tyr	15	.	.	B	.	.	.	.	.	0.76	.	*	.	0.84	0.80
	Val	16	.	.	B	.	.	.	.	.	0.61	.	.	.	0.07	0.59
20	Gly	17	.	.	.	.	.	T	T	.	0.57	.	.	.	0.20	0.36
	Asp	18	.	.	.	.	.	T	T	.	0.20	*	.	.	0.50	0.37
	Gly	19	.	.	.	.	.	.	T	C	0.23	*	.	.	0.30	0.27
	Leu	20	.	.	.	.	.	.	T	C	0.27	*	.	.	0.90	0.47
	Asn	21	.	.	.	.	.	.	.	C	1.12	*	.	.	0.70	0.43
25	Cys	22	.	A	B	.	.	.	.	.	1.47	*	.	.	0.30	0.76
	Glu	23	.	A	B	.	.	.	.	.	0.66	*	.	F	0.90	1.59
	Pro	24	A	A	.	.	.	.	.	.	0.79	.	.	F	0.75	0.81
	Glu	25	.	A	.	.	.	T	.	.	0.71	.	*	F	1.00	2.35
	Gln	26	A	A	.	.	.	.	.	.	0.71	.	.	F	0.45	0.95
30	Leu	27	A	A	.	.	.	.	.	.	1.49	*	.	F	0.60	1.03
	Pro	28	A	A	.	.	.	.	.	.	0.82	*	.	.	0.91	1.16
	Ile	29	.	.	B	.	.	.	.	.	0.22	*	.	.	0.82	0.36
	Asp	30	.	.	B	.	.	.	.	.	0.22	*	.	.	0.38	0.36
	Arg	31	.	.	B	.	.	.	.	.	0.22	*	.	.	1.14	0.40
35	Cys	32	.	.	B	.	.	.	.	.	1.03	*	.	.	1.60	0.96
	Leu	33	.	.	B	.	.	.	.	.	0.90	*	.	.	1.44	0.92
	Gln	34	.	.	.	.	.	T	T	.	1.79	*	.	F	2.03	0.47
	Asp	35	.	.	.	.	.	T	T	.	1.12	*	.	F	1.72	1.51
	Asn	36	.	.	.	.	.	T	T	.	0.98	*	*	F	1.41	0.98
40	Gly	37	.	.	.	.	.	T	T	.	1.06	*	*	F	1.25	0.77
	Gln	38	.	A	.	.	.	T	.	.	1.87	*	*	F	0.85	0.47
	Cys	39	A	A	.	.	.	.	.	.	1.28	.	*	.	0.30	0.48
	His	40	A	A	.	.	.	.	.	.	1.32	.	*	.	0.30	0.49
	Ala	41	A	A	.	.	.	.	.	.	0.66	.	*	.	0.60	0.57
45	Asp	42	A	A	.	.	.	.	.	.	0.14	.	*	.	0.30	0.57
	Ala	43	A	.	.	B	.	.	.	.	0.14	.	*	.	0.30	0.31
	Lys	44	A	.	.	B	.	.	.	.	0.00	.	*	.	0.60	0.51
	Cys	45	A	.	.	B	.	.	.	.	0.00	.	*	.	0.60	0.25

5	Val	46	A	.	.	B	.	.	-0.11	.	*	.	0.30	0.34
	Asp	47	A	.	.	B	.	.	-0.11	*	*	.	-0.30	0.15
	Leu	48	.	.	B	B	.	.	0.48	*	*	.	-0.60	0.48
	His	49	A	.	.	B	.	.	0.12	*	*	.	-0.15	1.08
	Phe	50	.	.	B	B	.	.	0.48	.	*	.	0.30	0.93
10	Gln	51	A	.	.	B	.	.	0.48	.	*	.	-0.15	1.63
	Asp	52	.	.	.	B	T	.	0.13	.	*	F	0.25	0.89
	Thr	53	.	.	.	B	T	.	0.09	.	.	F	0.40	1.01
	Thr	54	.	.	B	B	.	.	-0.58	*	.	F	-0.15	0.43
	Val	55	.	.	B	B	.	.	0.09	*	.	.	-0.60	0.23
15	Gly	56	.	.	B	B	.	.	-0.72	.	*	.	-0.60	0.21
	Val	57	.	.	B	B	.	.	-0.61	.	*	.	-0.60	0.12
	Phe	58	.	.	B	B	.	.	-0.60	.	*	.	-0.60	0.32
	His	59	.	.	B	B	.	.	-0.50	.	*	.	-0.60	0.43
	Leu	60	.	.	B	B	.	.	-0.46	.	*	.	-0.60	0.90
20	Arg	61	.	.	B	B	.	.	-0.46	.	*	F	-0.45	0.86
	Ser	62	.	.	.	.	T	C	0.40	.	*	F	0.45	0.63
	Pro	63	.	.	.	.	T	T	0.86	.	*	F	0.80	1.32
	Leu	64	.	.	.	.	T	T	0.93	.	*	F	0.80	1.05
	Gly	65	.	.	.	.	T	T	0.93	*	*	F	0.80	1.57
25	Gln	66	.	A	B	.	.	.	0.51	.	*	F	-0.15	0.84
	Tyr	67	.	A	B	.	.	.	0.11	.	*	F	-0.30	1.47
	Lys	68	.	A	B	.	.	.	0.32	.	*	.	-0.45	1.28
	Leu	69	.	A	B	.	.	.	1.18	*	*	.	-0.15	1.24
	Thr	70	.	A	B	.	.	.	0.93	.	*	.	0.45	1.58
30	Phe	71	A	A	.	.	.	.	1.04	*	*	.	0.60	0.80
	Asp	72	A	A	.	.	.	.	1.29	*	*	F	0.90	1.89
	Lys	73	A	A	.	.	.	.	0.66	*	*	F	0.90	2.27
	Ala	74	A	A	.	.	.	.	0.80	*	.	F	0.90	2.65
	Arg	75	A	A	.	.	.	.	0.52	*	.	F	0.75	0.85
35	Glu	76	A	A	.	.	.	.	1.22	*	.	F	0.75	0.43
	Ala	77	A	A	.	.	.	.	1.22	*	.	.	0.60	0.68
	Cys	78	A	A	.	.	.	.	0.59	.	*	.	0.60	0.60
	Ala	79	A	A	.	.	.	.	0.59	.	.	.	0.60	0.35
	Asn	80	A	A	.	.	.	.	0.17	.	.	.	0.30	0.35
40	Glu	81	A	A	.	.	.	.	-0.43	.	.	.	0.30	0.95
	Ala	82	A	A	.	.	.	.	-0.43	.	.	.	0.30	0.93
	Ala	83	A	A	.	.	.	.	-0.08	*	.	.	0.30	0.58
	Thr	84	A	A	.	.	.	.	0.27	.	.	.	-0.30	0.49
	Met	85	A	A	.	.	.	.	0.27	.	.	.	-0.60	0.76
45	Ala	86	A	A	.	.	.	.	0.27	.	.	.	-0.45	1.20
	Thr	87	A	.	.	.	T	.	0.04	.	.	.	-0.05	1.44
	Tyr	88	A	.	.	.	T	.	0.33	.	.	.	-0.05	1.20
	Asn	89	A	.	.	.	T	.	0.40	.	.	.	-0.05	1.60
	Gln	90	A	.	.	.	T	.	0.61	.	.	.	-0.05	1.73
	Leu	91	.	.	B	.	.	.	1.20	.	.	.	-0.25	1.41
	Ser	92	A	.	.	.	.	.	1.56	.	.	.	-0.25	1.52
	Tyr	93	A	A	.	.	.	.	1.21	.	*	.	-0.15	1.76
	Xxx	94	A	A	.	.	.	.	1.26	.	*	F	0.00	2.15

5	Gln	95	A	A	.	.	.	.	.	1.01	.	*	F	0.90	3.21
	Lys	96	A	A	.	.	.	.	.	1.79	.	*	F	0.60	3.21
	Ala	97	.	A	B	.	.	.	.	1.28	.	*	F	0.60	3.42
	Lys	98	.	A	B	.	.	.	.	0.86	.	*	F	0.60	1.63
	Tyr	99	.	A	B	.	.	.	.	0.94	*	*	.	-0.30	0.44
10	His	100	.	A	B	.	.	.	.	0.36	*	*	.	-0.30	0.58
	Leu	101	.	A	B	.	.	.	.	-0.03	.	*	.	-0.30	0.29
	Cys	102	.	A	B	.	.	.	.	0.27	.	*	.	-0.60	0.18
	Ser	103	.	.	B	.	.	T	.	-0.59	.	.	.	-0.20	0.14
	Ala	104	.	.	.	.	.	T	C	-0.34	.	.	.	0.00	0.14
15	Gly	105	.	.	.	.	T	T	.	-0.62	.	.	.	0.20	0.46
	Trp	106	A	.	.	.	.	T	.	-0.16	.	.	.	0.10	0.50
	Leu	107	A	.	.	.	.	.	.	0.62	*	*	.	-0.15	0.49
	Glu	108	.	.	B	.	.	T	.	0.07	*	.	F	1.35	0.96
	Thr	109	.	.	B	.	.	T	.	0.07	*	.	F	1.00	0.68
20	Gly	110	.	.	.	.	T	T	.	0.17	*	.	F	2.25	0.83
	Arg	111	.	.	.	.	T	T	.	0.24	*	.	F	2.50	0.75
	Val	112	.	.	B	.	.	.	.	0.74	*	.	.	0.90	0.81
	Ala	113	.	.	B	.	.	.	.	0.16	*	*	.	0.80	1.18
	Tyr	114	.	.	B	.	.	T	.	-0.23	.	*	.	0.60	0.61
25	Pro	115	.	.	B	.	.	T	.	-0.48	.	*	.	0.05	0.71
	Thr	116	.	.	B	.	.	T	.	-0.89	.	*	.	-0.20	0.71
	Ala	117	.	.	B	.	.	T	.	-0.03	.	.	.	-0.20	0.61
	Phe	118	.	.	B	.	.	.	.	0.56	.	.	.	-0.40	0.68
	Ala	119	.	.	B	.	.	.	.	0.13	.	.	.	-0.40	0.76
30	Ser	120	.	.	B	.	.	T	.	0.00	.	.	F	0.08	0.40
	Gln	121	.	.	.	.	.	T	.	0.01	.	.	F	0.61	0.46
	Asn	122	.	.	.	.	T	T	.	0.26	.	.	F	1.04	0.61
	Cys	123	.	.	.	.	T	T	.	0.10	.	.	F	1.77	0.45
	Gly	124	.	.	.	.	T	T	.	-0.17	.	.	F	1.30	0.19
35	Ser	125	.	.	.	.	T	T	.	-0.21	*	.	F	0.87	0.09
	Gly	126	.	.	B	.	.	T	.	-1.10	*	.	F	0.34	0.16
	Val	127	.	.	B	.	.	T	.	-1.96	*	.	.	0.06	0.12
	Val	128	.	.	B	B	.	.	.	-1.29	*	.	.	-0.47	0.06
	Gly	129	.	.	B	B	.	.	.	-1.19	*	.	.	-0.60	0.11
40	Ile	130	.	.	B	B	.	.	.	-1.23	*	.	.	-0.60	0.23
	Val	131	.	.	B	B	.	.	.	-1.10	*	*	.	-0.60	0.31
	Asp	132	.	.	B	.	.	T	.	-0.13	*	*	.	0.10	0.48
	Tyr	133	.	.	B	.	.	T	.	0.51	*	*	.	0.85	1.33
	Gly	134	.	.	B	.	.	T	.	0.86	*	*	F	1.34	2.78
45	Pro	135	.	.	.	.	.	T	C	1.79	*	*	F	2.18	2.68
	Arg	136	.	.	.	.	.	T	C	2.34	*	*	F	2.52	3.42
	Pro	137	.	.	.	.	.	T	C	2.34	*	*	F	2.86	4.63
	Asn	138	.	.	.	.	T	T	.	1.99	.	.	F	3.40	5.18
	Lys	139	.	.	.	.	.	T	C	2.04	.	.	F	2.86	2.62
	Ser	140	.	.	.	.	.	.	C	2.26	*	.	F	2.02	1.78
	Glu	141	.	.	B	.	.	.	.	1.29	*	.	F	1.78	1.85
	Met	142	A	.	B	B	.	.	.	0.80	.	.	.	0.64	0.69
	Trp	143	A	.	.	B	.	.	.	0.13	.	.	.	-0.30	0.44

	Asp	144	A	.	.	B	.	.	.	-0.16	.	.	.	-0.60	0.14
	Val	145	A	.	.	B	.	.	.	0.26	*	.	.	-0.60	0.22
	Phe	146	A	.	.	B	.	.	.	-0.34	*	*	.	-0.60	0.40
	Cys	147	A	.	.	B	.	.	.	0.30	*	*	.	-0.30	0.24
5	Tyr	148	A	.	.	.	.	.	.	0.59	*	.	.	0.21	0.65
	Arg	149	.	.	.	.	T	.	.	-0.27	*	.	.	1.67	1.25
	Met	150	.	.	.	.	T	.	.	0.59	.	.	.	1.98	1.73
	Lys	151	.	.	.	.	T	.	.	0.62	*	*	F	2.74	1.77
10	Asp	152	.	.	.	.	T	T	.	0.98	.	.	F	3.10	0.48
	Val	153	A	.	.	.	.	T	.	0.83	.	*	F	2.09	0.71
	Asn	154	.	.	B	.	.	T	.	0.77	.	*	.	1.63	0.45
	Cys	155	.	.	B	.	.	T	.	0.51	*	*	.	1.32	0.54
	Thr	156	.	.	B	B	.	.	.	0.12	*	*	F	0.16	0.54
	Xxx	157	.	.	B	B	.	.	.	-0.12	.	*	F	0.45	0.33
15	Lys	158	.	.	B	B	.	.	.	-0.12	*	*	F	-0.15	0.97
	Val	159	.	.	B	B	.	.	.	-0.47	*	*	.	-0.30	0.50
	Gly	160	.	.	B	B	.	.	.	0.20	.	*	.	-0.30	0.39
	Tyr	161	.	.	B	B	.	.	.	0.17	*	.	.	0.30	0.32
	Val	162	.	.	B	.	.	T	.	-0.14	*	.	.	0.10	0.43
20	Gly	163	.	.	B	.	.	T	.	-0.49	*	.	.	-0.20	0.38
	Asp	164	.	.	B	.	.	T	.	0.12	*	.	.	-0.20	0.32
	Gly	165	.	.	B	.	.	T	.	0.17	*	.	.	-0.20	0.68
	Phe	166	.	.	B	.	.	.	.	0.07	*	.	.	-0.10	0.92
	Ser	167	.	.	B	.	.	.	.	0.92	*	*	.	-0.10	0.55
25	Tyr	168	.	.	.	.	T	T	.	0.46	*	.	.	0.20	0.89
	Ser	169	.	.	.	.	.	T	C	-0.36	*	.	F	0.15	0.85
	Gly	170	.	.	.	.	T	T	.	-0.01	*	.	F	0.35	0.52
	Asn	171	.	.	.	.	.	T	C	-0.17	*	.	F	0.15	0.58
30	Leu	172	.	.	B	B	.	.	.	-0.68	*	.	.	-0.60	0.32
	Leu	173	.	.	B	B	.	.	.	-1.03	*	.	.	-0.60	0.27
	Gln	174	.	.	B	B	.	.	.	-1.03	*	.	.	-0.60	0.16
	Val	175	.	.	B	B	.	.	.	-1.39	*	.	.	-0.60	0.27
	Leu	176	.	.	B	B	.	.	.	-1.60	*	.	.	-0.60	0.28
	Met	177	.	.	B	B	.	.	.	-1.09	*	.	.	-0.60	0.25
35	Ser	178	.	.	B	B	.	.	.	-1.09	*	*	.	-0.60	0.45
	Phe	179	.	.	B	.	.	T	.	-1.40	*	.	.	-0.20	0.45
	Pro	180	.	.	.	.	.	T	C	-0.54	*	.	.	0.00	0.66
	Ser	181	.	.	.	.	.	T	C	-0.43	*	.	F	0.15	0.79
	Leu	182	.	.	.	.	.	T	C	-0.64	*	.	F	0.15	0.79
40	Thr	183	.	.	.	.	.	.	C	-0.66	*	.	F	-0.05	0.42
	Asn	184	.	.	.	.	.	.	C	0.04	*	.	.	-0.20	0.45
	Phe	185	A	A	.	.	.	.	.	-0.60	*	.	.	-0.60	0.95
	Leu	186	.	A	B	.	.	.	.	-1.11	*	.	.	-0.60	0.49
	Thr	187	.	A	B	.	.	.	.	-0.89	*	.	.	-0.60	0.25
45	Glu	188	.	A	B	.	.	.	.	-0.82	*	.	.	-0.60	0.29
	Val	189	A	A	.	.	.	.	.	-1.12	*	.	.	-0.60	0.56
	Leu	190	.	A	B	.	.	.	.	-0.42	*	.	.	-0.60	0.52
	Ala	191	A	A	.	.	.	.	.	0.09	.	.	.	-0.30	0.48
	Tyr	192	A	.	.	.	.	T	.	0.10	.	.	.	0.10	0.86

5	Ser	193	.	.	.	.	.	T	C	-0.49	*	*	F	0.90	1.40
	Asn	194	.	.	.	.	.	T	C	0.48	*	*	F	1.50	1.40
	Ser	195	.	.	.	.	.	T	C	0.94	.	*	F	2.40	1.76
	Ser	196	.	.	.	.	.	T	C	1.64	.	*	F	3.00	1.30
	Ala	197	.	.	.	.	.	T	C	1.30	.	*	F	2.70	1.58
10	Arg	198	A	.	.	.	.	T	.	0.90	.	*	F	2.20	1.19
	Gly	199	A	.	.	.	.	T	.	0.09	.	*	F	1.45	0.77
	Arg	200	A	A	.	.	.	.	.	0.39	.	*	F	0.75	0.63
	Ala	201	A	A	.	.	.	.	.	0.66	*	*	.	0.60	0.56
	Phe	202	A	A	.	.	.	.	.	0.43	*	*	.	0.30	0.76
15	Leu	203	A	A	.	.	.	.	.	0.01	*	*	.	-0.30	0.32
	Glu	204	A	A	.	.	.	.	.	0.36	*	*	.	-0.60	0.46
	His	205	A	A	.	.	.	.	.	-0.57	*	*	.	-0.30	0.89
	Leu	206	A	A	.	.	.	.	.	-0.28	*	*	.	-0.30	0.89
	Thr	207	A	A	.	.	.	.	.	-0.47	*	*	F	0.45	0.69
20	Asp	208	A	A	.	.	.	.	.	0.46	*	*	F	-0.45	0.35
	Leu	209	A	A	.	.	.	.	.	0.11	*	*	.	0.30	0.84
	Ser	210	.	.	B	B	.	.	.	-0.17	*	*	F	0.45	0.57
	Ile	211	.	.	B	B	.	.	.	-0.17	.	*	F	0.45	0.50
	Arg	212	.	.	B	B	.	.	.	-0.56	.	*	F	-0.15	0.50
25	Gly	213	.	.	B	B	.	.	.	-1.41	.	*	F	-0.45	0.32
	Thr	214	.	.	B	B	.	.	.	-0.81	.	*	F	-0.45	0.34
	Leu	215	.	.	B	B	.	.	.	-0.51	*	*	.	-0.60	0.27
	Phe	216	.	.	B	B	.	.	.	0.38	*	*	.	-0.60	0.47
	Val	217	.	.	B	B	.	.	.	-0.03	.	*	F	-0.45	0.52
30	Pro	218	.	.	B	B	.	.	.	-0.03	.	.	F	-0.45	0.85
	Gln	219	.	.	.	.	T	.	.	-0.53	.	.	F	0.15	0.97
	Asn	220	.	.	.	.	.	T	C	-0.07	.	.	F	0.60	1.08
	Ser	221	.	.	.	.	.	T	C	0.63	.	.	F	0.45	0.69
	Gly	222	.	.	.	.	.	T	C	1.49	.	.	F	1.05	0.69
35	Leu	223	.	.	.	.	.	T	C	1.70	.	.	F	1.05	0.69
	Gly	224	.	.	.	.	.	.	C	1.39	.	.	F	1.15	0.89
	Glu	225	.	.	B	.	.	.	.	0.58	.	.	F	1.10	1.30
	Asn	226	.	.	B	.	.	.	.	0.58	.	.	F	0.80	1.30
	Glu	227	.	.	B	.	.	.	.	0.58	.	*	F	1.10	1.76
40	Thr	228	A	.	.	.	.	.	.	1.50	*	*	F	1.10	1.01
	Leu	229	A	.	.	.	.	T	.	1.84	*	.	F	1.30	1.23
	Ser	230	A	.	.	.	.	T	.	0.96	*	.	F	1.30	1.18
	Gly	231	A	.	.	.	.	T	.	0.96	*	.	F	0.85	0.57
	Arg	232	A	.	.	.	.	T	.	0.92	*	.	F	1.30	1.21
45	Asp	233	A	A	.	.	.	.	.	1.20	*	*	F	0.90	1.23
	Ile	234	A	A	.	.	.	.	.	1.20	*	.	F	0.90	1.69
	Glu	235	A	A	.	.	.	.	.	0.91	*	.	.	0.60	0.71
	His	236	A	A	.	.	.	.	.	1.26	*	.	.	0.30	0.43
	His	237	A	A	.	.	.	.	.	0.29	*	.	.	-0.30	0.98
	Leu	238	A	.	.	B	.	.	.	-0.01	*	*	.	-0.30	0.42
	Ala	239	A	.	.	B	.	.	.	0.28	*	.	.	-0.60	0.42
	Asn	240	A	.	.	B	.	.	.	-0.42	*	.	.	-0.60	0.30
	Val	241	A	.	.	B	.	.	.	-1.09	*	.	.	-0.60	0.32

5	Ser	242	A	.	B	B	.	.	.	-1.30	*	.	.	-0.60	0.27
	Met	243	.	.	B	B	.	.	.	-0.49	*	.	.	-0.60	0.27
	Phe	244	.	.	B	B	.	.	.	0.10	*	*	.	-0.60	0.57
	Phe	245	.	.	B	B	.	.	.	-0.71	.	.	.	-0.60	0.72
	Tyr	246	.	.	B	.	.	T	.	-0.71	.	.	.	-0.20	0.60
10	Asn	247	.	.	B	.	.	T	.	-0.41	.	.	.	-0.20	0.51
	Asp	248	.	.	.	.	T	T	.	-0.16	.	.	.	0.20	0.95
	Leu	249	.	.	.	.	.	T	C	0.23	*	.	.	0.30	0.60
	Val	250	.	.	.	.	T	T	C	0.62	*	.	F	0.65	0.54
	Asn	251	.	.	.	.	T	T	.	0.06	.	.	F	0.65	0.47
15	Gly	252	.	.	.	.	.	T	C	0.06	.	.	F	0.15	0.47
	Thr	253	.	.	B	.	.	T	.	-0.26	*	*	F	0.10	1.09
	Thr	254	.	.	B	B	.	.	.	0.67	*	*	F	-0.15	0.97
	Leu	255	.	.	B	B	.	.	.	0.71	.	*	F	0.60	1.93
	Gln	256	.	.	B	B	.	.	.	0.37	*	*	F	0.00	1.10
20	Thr	257	.	.	B	B	.	.	.	0.41	*	*	F	-0.15	0.76
	Arg	258	.	.	B	B	.	.	.	0.77	*	*	F	0.00	1.23
	Leu	259	.	.	B	B	.	.	.	0.27	*	*	F	0.90	1.42
	Gly	260	.	.	.	B	T	.	.	0.27	*	*	F	0.85	0.81
	Ser	261	.	.	.	B	.	.	C	-0.62	*	*	F	0.65	0.34
25	Lys	262	.	.	B	B	.	.	.	-0.62	*	*	F	-0.45	0.29
	Leu	263	.	.	B	B	.	.	.	-0.73	*	*	F	-0.15	0.42
	Leu	264	.	.	B	B	.	.	.	0.19	*	*	.	0.64	0.53
	Ile	265	.	.	B	B	.	.	.	0.53	.	*	.	0.98	0.52
	Thr	266	.	.	B	.	.	T	.	0.83	.	*	F	2.02	1.08
30	Asp	267	.	.	B	.	.	T	.	0.58	.	*	F	2.66	2.19
	Arg	268	.	.	.	.	T	T	.	0.58	.	.	F	3.40	4.84
	Gln	269	.	.	B	.	.	T	.	1.36	.	.	F	2.66	2.77
	Asp	270	.	.	.	.	.	.	C	2.03	.	.	F	2.32	2.25
	Pro	271	.	.	.	.	.	.	C	2.03	.	.	F	1.98	1.78
35	Leu	272	.	.	.	.	.	.	C	2.03	.	.	F	1.34	1.48
	His	273	.	.	.	.	.	T	C	1.61	.	.	F	1.20	1.54
	Pro	274	.	.	.	.	.	T	C	1.72	.	*	F	0.60	1.43
	Thr	275	.	.	.	.	T	T	.	1.06	*	.	F	1.40	3.41
	Glu	276	.	.	B	.	.	T	.	0.41	*	.	F	1.30	1.34
40	Thr	277	.	.	B	.	.	.	.	1.22	*	.	F	0.96	0.64
	Arg	278	.	.	B	.	.	.	.	0.91	.	*	F	1.57	0.75
	Cys	279	.	.	B	.	.	T	.	1.23	.	.	.	1.93	0.43
	Val	280	.	.	B	.	.	T	.	1.54	.	.	F	2.39	0.58
	Asp	281	.	.	.	.	T	T	.	1.23	.	*	F	3.10	0.49
45	Gly	282	.	.	.	.	T	T	.	0.73	.	*	F	2.94	1.33
	Arg	283	.	A	.	.	T	.	.	0.62	.	*	F	2.23	1.47
	Asp	284	.	A	.	.	T	.	.	1.00	.	*	F	1.92	1.53
	Thr	285	A	A	.	.	.	.	.	1.86	.	*	F	0.91	1.63
	Leu	286	A	A	.	.	.	.	.	0.97	.	*	.	0.75	1.39
	Glu	287	A	A	.	.	.	.	.	0.64	.	*	.	0.30	0.58
	Trp	288	.	A	B	B	.	.	.	-0.06	.	*	.	-0.30	0.22
	Asp	289	A	A	.	B	.	.	.	-0.36	.	*	.	-0.30	0.26
	Ile	290	A	A	.	B	.	.	.	-0.04	.	*	.	-0.30	0.20

	Cys	291	A	A	.	B	.	.	.	0.42	.	*	.	-0.47	0.31
	Ala	292	.	.	.	.	T	T	.	-0.47	.	*	.	1.36	0.19
	Ser	293	.	.	.	.	T	T	.	-0.49	.	*	F	0.74	0.19
	Asn	294	.	.	.	.	T	T	.	-0.52	.	.	F	0.87	0.50
5	Gly	295	.	.	.	.	T	T	.	-0.49	*	.	F	1.30	0.67
	Ile	296	.	.	B	B	.	.	.	-0.71	*	.	F	0.07	0.37
	Thr	297	.	.	B	B	.	.	.	-0.42	*	.	.	-0.21	0.16
	His	298	.	.	B	B	.	.	.	-0.01	*	.	.	-0.34	0.22
	Val	299	.	.	B	B	.	.	.	-0.40	*	.	.	-0.17	0.61
10	Ile	300	.	.	B	B	.	.	.	-0.87	*	.	.	-0.04	0.54
	Ser	301	.	.	B	B	.	.	.	0.07	*	.	.	0.22	0.33
	Arg	302	.	.	B	B	.	.	.	-0.21	*	.	.	1.08	0.89
	Xxx	303	.	.	.	B	T	.	.	-0.39	*	.	F	2.04	1.28
	Leu	304	.	.	.	B	T	.	.	0.26	*	.	F	2.60	1.48
15	Lys	305	.	.	.	B	.	.	C	0.56	*	.	F	2.14	1.17
	Ala	306	.	.	.	.	.	.	C	0.64	*	.	F	1.63	0.92
	Pro	307	.	.	.	.	.	.	C	-0.32	*	.	F	1.52	1.73
	Pro	308	.	.	.	.	.	.	C	-0.24	.	*	F	1.11	0.64
	Ala	309	.	.	B	B	.	.	.	-0.24	.	*	F	-0.45	0.92
20	Pro	310	.	.	B	B	.	.	.	-0.68	.	.	.	-0.60	0.49
	Val	311	.	.	B	B	.	.	.	-0.12	.	.	.	-0.60	0.40
	Thr	312	.	.	B	B	.	.	.	-0.22	.	.	.	-0.60	0.54
	Leu	313	.	.	B	B	.	.	.	-0.36	.	.	.	-0.60	0.51
	Xxx	314	.	.	B	B	.	.	.	-0.58	.	.	.	-0.60	0.68
25	His	315	.	.	B	B	.	.	.	-0.71	.	.	F	-0.60	0.39
	Thr	316	.	.	B	B	.	.	.	-0.24	.	.	F	-0.45	0.46
	Gly	317	.	.	.	.	.	.	C	-0.28	.	.	F	0.25	0.46
	Leu	318	.	.	.	.	.	.	C	-0.36	.	.	F	0.25	0.34
	Gly	319	.	.	.	.	T	T	.	-0.67	.	.	F	0.35	0.16
30	Xxx	320	.	.	.	.	.	T	C	-1.02	.	.	.	0.00	0.14
	Gly	321	.	.	B	.	.	T	.	-1.10	*	.	.	-0.20	0.22
	Ile	322	.	.	B	.	.	T	.	-1.64	.	.	.	-0.20	0.29
	Phe	323	.	.	B	B	.	.	.	-1.72	.	.	.	-0.60	0.16
	Xxx	324	.	.	B	B	.	.	.	-2.19	.	.	.	-0.60	0.11
35	Xxx	325	.	.	B	B	.	.	.	-2.66	.	.	.	-0.60	0.13
	Ile	326	.	.	B	B	.	.	.	-2.62	.	.	.	-0.60	0.11
	Ile	327	.	.	B	B	.	.	.	-2.08	.	.	.	-0.60	0.13
	Leu	328	.	.	B	B	.	.	.	-1.97	.	.	.	-0.60	0.10
	Val	329	.	.	B	B	.	.	.	-2.43	.	.	.	-0.60	0.14
40	Thr	330	.	.	B	B	.	.	.	-2.63	.	.	.	-0.60	0.15
	Gly	331	A	.	.	B	.	.	.	-2.56	.	.	.	-0.60	0.18
	Ala	332	A	.	.	B	.	.	.	-2.26	.	.	.	-0.60	0.20
	Val	333	A	.	.	B	.	.	.	-2.03	.	.	.	-0.60	0.14
	Ala	334	A	.	.	B	.	.	.	-1.42	.	.	.	-0.60	0.15
45	Leu	335	A	.	.	B	.	.	.	-1.41	.	.	.	-0.60	0.23
	Ala	336	A	.	.	B	.	.	.	-1.31	.	.	.	-0.60	0.41
	Ala	337	A	.	.	B	.	.	.	-1.42	*	*	.	-0.60	0.63
	Tyr	338	A	.	.	B	.	.	.	-0.46	*	*	.	-0.60	0.67
	Ser	339	A	.	.	B	.	.	.	-0.76	.	*	.	-0.45	1.29

	Tyr	340	.	.	B	B	.	.	.	0.06	*	*	.	-0.60	0.90
	Phe	341	.	.	B	B	.	.	.	0.76	*	*	.	-0.26	0.92
	Arg	342	.	.	B	B	.	.	.	1.39	*	*	.	0.53	1.35
	Ile	343	.	.	B	B	.	.	.	1.32	*	*	.	1.47	1.72
5	Asn	344	.	.	B	.	.	T	.	0.73	*	*	F	2.66	2.86
	Arg	345	.	.	.	.	T	T	.	0.63	*	*	F	3.40	1.02
	Lys	346	.	.	.	.	T	T	.	0.63	*	*	F	2.76	1.45
	Thr	347	.	.	.	.	T	T	.	0.13	*	*	F	2.27	0.78
	Ile	348	.	.	B	.	.	.	.	0.99	*	.	F	1.33	0.51
10	Gly	349	.	.	B	.	.	.	.	0.29	.	.	.	0.24	0.35
	Phe	350	.	A	B	.	.	.	.	-0.21	.	.	.	-0.60	0.21
	Xxx	351	.	A	B	.	.	.	.	-0.64	.	.	.	-0.60	0.38
	His	352	.	A	B	.	.	.	.	-0.72	.	.	.	-0.60	0.49
15	Phe	353	.	A	B	.	.	.	.	-0.22	.	.	.	-0.60	0.72

Among highly preferred fragments in this regard are those that comprise regions of WF-HABP, OE-HABP, and BM-HABP that combine several structural features, such as several of the features set out above.

Other preferred fragments are biologically active WF-HABP, OE-HABP, and BM-HABP fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the WF-HABP, OE-HABP, and BM-HABP polypeptides. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

The WF-HABP, OE-HABP, and BM-HABP inventions also provide polypeptides comprising epitope-bearing portions of the polypeptides of the invention. The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NOs: 2, 5, 8, or 11, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit Nos. 203501, 203502, and 203503, or encoded by a polynucleotide that hybridizes to the complement of the sequence of SEQ ID NOs: 2, 5, 8, or 11, or contained in ATCC deposit Nos. 203501, 203502, and 203503 under stringent hybridization conditions or lower stringency hybridization conditions as defined supra. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NOs: 2, 5, 8, 11),



polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or lower stringency hybridization conditions defined supra.

5       The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an  
10   animal, as determined by any method known in the art, for example, by the methods for generating antibodies described infra. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays  
15   described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross-reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

      Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985), further described in  
20   U.S. Patent No. 4,631,211).

      In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides  
25   comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include  
30   the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, in vivo immunization, in vitro immunization, and phage display methods. See, e.g., Sutcliffe et al., supra; Wilson et al., supra, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If in vivo immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 µg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention comprising an immunogenic or antigenic epitope can be fused to other

polypeptide sequences. For example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof) resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life in vivo. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., *Nature*, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., *J. Biochem.*, 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:8972-897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni<sup>2+</sup> nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., *Curr. Opin. Biotechnol.* 8:724-33 (1997); Harayama, *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, et al., *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo and Blasco, *Biotechniques* 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by

reference in its entirety). In one embodiment, alteration of polynucleotides corresponding to SEQ ID NOs: 1, 4, 7, or 10, and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

Non-limiting examples of antigenic polypeptides that can be used to generate full-length WF-HABP receptor-specific antibodies include: a polypeptide comprising amino acid residues: from M-1 to I9, from D-3 to T12, from F-26 to L-35, from I-50 to T-59, from T-54 to W-63, from S-81 to Q-90, from P-117 to P-124, from G-122 to Q-130, from S-152 to F-160, from P-165 to L-173, from D-171 to I-179, from K-207 to L-215, from N-225 to L-234, from P-270 to H-278, from H-272 to I-280, from T-295 to L-303, from D-304 to Y-312, from V-321 to Y-329, from E-336 to F-344, from P-346 to G-354, from C-359 to D-367, from S-366 to A-374, from F-378 to C-386, from S-390 to Q-398, from Q-398 to V-406, from C-410 to G-418, from R-432 to D-440, from M-438 to L-446, from V-457 to C-465, from R-464 to E-472, from G-470 to C-478, from C-484 to C-492, from S-493 to G-501, from G-513 to C-521, from D-525 to G-533, from G-528 to H-536, from G-545 to L-554, from G-556 to C-564, from S-565 to G-573, from C-570 to H-578, from L-602 to A-610, from Q-620 to F-628, from Q-631 to V-639, from L-648 to L-656, from L-653 to V-661, from N-665 to R-673, from W-670 to R-678, from P-707 to G-715, from T-756 to G-764, from S-767 to R-775, from T-788 to N-796, from N-809 to N-816, from L-826 to I-834, from E-853 to N-861, from C-862 to Q-870, from Q-875 to V-883, from S-889 to T-897, from A-899 to C-907, from C-916 to G-924, from G-929 to F-937, from F-937 to C-945, from L-959 to T-967, from Q-978 to S-986, from R-977 to P-1005, from Q-1006 to N-1014, from V-1018 to T-1026, from E-1042 to H-1050, from K-1061 to C-1069, from D-1073 to L-1081, from C-1111 to G-1119, from G-1119 to T-1124, from E-1126 to N-1134, from C-1131 to S-1139, from C-1144 to R-1152, from T-1147 to T-1155, from L-1176 to F-1184, from K-1193 to F-1201, from M-1211 to L-1219. G-1236 to D-1244, from L-1240 to Q-1248, from R-1260 to

I-1268, from V-1277 to N-1285, from H-1302 to I-1310, from D-1307 to V-1315, from L-1340 to F-1348, from A-1360 to W-1368, from H-1371 to A-1379, from S-1414 to E-1422, from M-1424 to I-1432, from G-1426 to Q-1434, from P-1453 to D-1461, from F-1463 to N-1471, from P-1480 to E-1488, from Q-1487 to C-1495, from G-1524 to G-1532, from L-1529 to C-1537, from W-1542 to H-1550, from G-1549 to A-1557, from P-1559 to S-1567, from P-1565 to M-1573, from M-1573 to Q-1581, from G-1614 to G-1622, from D-1617 to S-1625, from F-1627 to P-1635, from E-1630 to E-1638, from A-1655 to C-1163, from L-1667 to V-1675, from L-1681 to C-1689, from C-1689 to Q-1697, from L-1707 to W-1715, from C-1717 to D-1725, from D-1725 to E-1733, from S-1739 to C-1747, from G-1741 to C-1749, from L-1761 to D-1769, from G-1773 to D-1781, from H-1788 to V-1796, from A-1860 to G-1868, from G-1873 to R-1881. K-1876 to A-1884, from A-1893 to V-1901, from S-1906 to D-1914, from N-1734 to F-1942, from D-1944 to Y-1952, from S-1970 to A-1978, from D-1973 to A-1981, from N-1987 to D-1995, from S-2005 to S-2013, from L-2085 to G-2093, from Q-2100 to D-2108, from D-2103 to P-2111, from W-2112 to L-2120, from P-2136 to E-2144, from E-2143 to R-2151, from Cys-359 to Gly-363, from Pro-392 to His-395, from Pro-414 to Ser-416, from Pro-487 to Gly-490, from Ser-515 to Asp-517, from Asn-574 to Gly-576, from Pro-708 to Gly-710, from Gln-1006 to Cys-1011, from Arg-1114 to Ser-1118, from Cys-1131 to Gly-1137, from Ser-1146 to Gly-1150, from Pro-1305 to Asp-1307, from Pro-1565 to Asp-1568, from Glu-1670 to Gly-1673, from Asp-1684 to Gly-1688, from Pro-1708 to Gly-1714, from Pro-1722 to about Gly-1726, from Asp-2010 to Ser-2013. of SEQ ID NO:2. In further preferred embodiments, polypeptide fragments of the invention compose 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, or 20 of the above recited full-length WF-HABP antigenic regions. As indicated above, the inventors have determined that the above polypeptide fragments are antigenic regions of the full-length WF-HABP polypeptide.

Non-limiting examples of antigenic polypeptides that can be used to generate WF-HABP receptor-specific antibodies include: a polypeptide comprising amino acid residues: from L-7 to W-15, from C-17 to D-25, from G-26 to H-34, from S-39 to C-47, from L-42 to H-50, from L-61 to D-69, from P-75 to M-83, from H-88 to V-96, from V-159 to V-167, from G-173 to R-181, from N-177 to Y-185, from A-193 to V-201, from T-207 to V-215, from N-234 to F-242, from D-244 to Y-252, from V-259 to M-267, from N-287 to P-295, from S-305 to S-313, from L-386 to G-394, from D-404 to P-412, from W-413 to L-421, from E-436 to E-444, from and/or from E-445 to I-453 of SEQ ID NO:5. In further preferred embodiments, polypeptide fragments of the invention compose 2, 3, 4, 5, 6, 7, 8, 9, 10, 15,

or 20 of the above recited WF-HABP antigenic regions. As indicated above, the inventors have determined that the above polypeptide fragments are antigenic regions of the WF-HABP polypeptide.

Non-limiting examples of antigenic polypeptides that can be used to generate OE-HABP receptor-specific antibodies include: a polypeptide comprising amino acid residues: from Y-26 to N-34, from N-37 to N-45, from V-50 to L-58, from L-78 to V-86, from K-90 to E-98, from N-94 to L-102, from L-107 to Y-115, from R-110 to R-118, from V-119 to H-127, from K-125 to I-133, from L-136 to Y-144, from Y-141 to V-148, from D-150 to L-158, from Y-170 to Q-178, A204 to C-212, from R-230 to L-238, from S-244 to L-252, from H-249 to V-257, from and/or A-282 to K-289 of SEQ ID NO:8. In further preferred embodiments, polypeptide fragments of the invention compose 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, or 20 of the above recited OE-HABP antigenic regions. As indicated above, the inventors have determined that the above polypeptide fragments are antigenic regions of the OE-HABP polypeptide.

Non-limiting examples of antigenic polypeptides that can be used to generate BM-HABP receptor-specific antibodies include: a polypeptide comprising amino acid residues: from T-2 to E-10, from H-7 to Y-15, from G-17 to E-25, from C-22 to D-30, from R-31 to C-39, from R-61 to L-69, from T-70 to C-78, from R-75 to H-83, from Y-93 to L-101, from L-107 to P-115, from S-120 to V-128, from Y-133 to E-141, from P-135 to W-143, from Y-148 to T-156, from S-193 to A-201, from S-195 to L-203, from N-220 to T-228, from L-229 to H-237, from L-264 to L-272, from P-271 to C-279, from C-279 to E-287, from A-292 to I-296, from S-301 to A-309, from and/or R-342 to F-350 of SEQ ID NO:11. In further preferred embodiments, polypeptide fragments of the invention compose 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, or 20 of the above recited BM-HABP antigenic regions. As indicated above, the inventors have determined that the above polypeptide fragments are antigenic regions of the BM-HABP polypeptide.

For many proteins, it is known in the art that one or more amino acids may be deleted from the N-terminus or C-terminus without substantial loss of biological function. However, even if deletion of one or more amino acids from the N-terminus or C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other full-length WF-HABP functional activities may still be retained. For example, in many instances, the ability of the shortened protein to induce and/or bind to antibodies which recognize the full-length WF-HABP (preferably antibodies that bind specifically to the full-length WF-HABP)

will be retained irrespective of the size or location of the deletion. Whether a particular polypeptide lacking N-terminal and/or C-terminal residues of a complete protein retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

5 For many proteins, it is known in the art that one or more amino acids may be deleted from the N-terminus or C-terminus without substantial loss of biological function. However, even if deletion of one or more amino acids from the N-terminus or C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other WF-HABP functional activities may still be retained. For example, in many instances, the ability of  
10 the shortened protein to induce and/or bind to antibodies which recognize WF-HABP (preferably antibodies that bind specifically to WF-HABP) will be retained irrespective of the size or location of the deletion. Whether a particular polypeptide lacking N-terminal and/or C-terminal residues of a complete protein retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

15 For many proteins, it is known in the art that one or more amino acids may be deleted from the N-terminus or C-terminus without substantial loss of biological function. However, even if deletion of one or more amino acids from the N-terminus or C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other OE-HABP functional activities may still be retained. For example, in many instances, the ability of  
20 the shortened protein to induce and/or bind to antibodies which recognize OE-HABP (preferably antibodies that bind specifically to OE-HABP) will be retained irrespective of the size or location of the deletion. Whether a particular polypeptide lacking N-terminal and/or C-terminal residues of a complete protein retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

25 For many proteins, it is known in the art that one or more amino acids may be deleted from the N-terminus or C-terminus without substantial loss of biological function. However, even if deletion of one or more amino acids from the N-terminus or C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other BM-HABP functional activities may still be retained. For example, in many instances, the ability of  
30 the shortened protein to induce and/or bind to antibodies which recognize BM-HABP (preferably antibodies that bind specifically to BM-HABP) will be retained irrespective of the size or location of the deletion. Whether a particular polypeptide lacking N-terminal and/or C-

terminal residues of a complete protein retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

In one embodiment, the present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of the full-length

5 WF-HABP polypeptide depicted in Figures 1A-H (SEQ ID NO:2). Particularly, in one embodiment, N-terminal deletions of the full-length WF-HABP polypeptide can be described by the general formula m to 2156, where m is an integer from 1 to 2155 corresponding to the position of amino acids identified in SEQ ID NO:2 and preferably, corresponds to one of the N-terminal amino acid residues identified in the N-terminal deletions specified herein. In

10 specific embodiments, N-terminal deletions of the full-length WF-HABP polypeptide of the invention comprise, or alternatively, consist of, amino acid residues: M-2 to K-2157; D-3 to K-2157; Q-4 to K-2157; G-5 to K-2157; C-6 to K-2157; R-7 to K-2157; E-8 to K-2157; I-9 to K-2157; L-10 to K-2157; T-11 to K-2157; T-12 to K-2157; A-13 to K-2157; G-14 to K-2157; P-15 to K-2157; F-16 to K-2157; T-17 to K-2157; V-18 to K-2157; L-19 to K-2157; V-20 to K-2157; P-21 to K-2157; S-22 to K-2157; V-23 to K-2157; S-24 to K-2157; S-25 to K-2157; F-26 to K-2157; S-27 to K-2157; S-28 to K-2157; R-29 to K-2157; T-30 to K-2157; M-31 to K-2157; N-32 to K-2157; A-33 to K-2157; S-34 to K-2157; L-35 to K-2157; A-36 to K-2157; Q-37 to K-2157; Q-38 to K-2157; L-39 to K-2157; C-40 to K-2157; R-41 to K-2157; Q-42 to K-2157; H-43 to K-2157; I-44 to K-2157; I-45 to K-2157; A-46 to K-2157; G-47 to K-2157; Q-48 to K-2157; H-49 to K-2157; I-50 to K-2157; L-51 to K-2157; E-52 to K-2157; D-53 to K-2157; T-54 to K-2157; R-55 to K-2157; T-56 to K-2157; Q-57 to K-2157; Q-58 to K-2157; T-59 to K-2157; R-60 to K-2157; R-61 to K-2157; W-62 to K-2157; W-63 to K-2157; T-64 to K-2157; L-65 to K-2157; A-66 to K-2157; G-67 to K-2157; Q-68 to K-2157; E-69 to K-2157; I-70 to K-2157; T-71 to K-2157; V-72 to K-2157; T-73 to K-2157; F-74 to K-2157; N-75 to K-2157; Q-76 to K-2157; F-77 to K-2157; T-78 to K-2157; K-79 to K-2157; Y-80 to K-2157; S-81 to K-2157; Y-82 to K-2157; K-83 to K-2157; Y-84 to K-2157; K-85 to K-2157; D-86 to K-2157; Q-87 to K-2157; P-88 to K-2157; Q-89 to K-2157; Q-90 to K-2157; T-91 to K-2157; F-92 to K-2157; N-93 to K-2157; I-94 to K-2157; Y-95 to K-2157; K-96 to K-2157; A-97 to K-2157; N-98 to K-2157; N-99 to K-2157; I-100 to K-2157; A-101 to K-2157; A-102 to K-2157; N-103 to K-2157; G-104 to K-2157; V-105 to K-2157; F-106 to K-2157; H-107 to K-2157; V-108 to K-2157; V-109 to K-2157; T-110 to K-2157; G-111 to K-2157; L-112 to K-2157; R-113 to K-2157; W-114 to K-2157; Q-115 to K-2157; A-116 to K-2157; P-117 to K-2157; S-118 to K-2157; G-119 to K-2157; T-120 to K-2157; P-121 to K-2157; G-122 to K-



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Further embodiments of the invention are directed to C-terminal deletions of the full-length WF-HABP polypeptide described by the general formula 1 to n, where n is an integer from 2-2157 corresponding to the position of amino acid residue identified in SEQ ID NO:2 and preferably, corresponds to one of the C-terminal amino acid residues identified in the C-terminal deletions specified herein. In specific embodiments, C terminal deletions of the full-

length WF-HABP polypeptide of the invention comprise, or alternatively, consist of, amino acid residues: M-1 to V-2156; M-1 to T-2155; M-1 to L-2154; M-1 to I-2153; M-1 to R-2152; M-1 to Q-2151; M-1 to T-2150; M-1 to D-2149; M-1 to P-2148; M-1 to F-2147; M-1 to D-2146; M-1 to E-2145; M-1 to E-2144; M-1 to L-2143; M-1 to L-2142; M-1 to S-2141; M-1 to D-2140; M-1 to D-2139; M-1 to F-2138; M-1 to P-2137; M-1 to E-2136; M-1 to C-2135; M-1 to F-2134; M-1 to T-2133; M-1 to D-2132; M-1 to S-2131; M-1 to G-2130; M-1 to F-2129; M-1 to V-2128; M-1 to P-2127; M-1 to N-2126; M-1 to P-2125; M-1 to V-2124; M-1 to X-2123; M-1 to V-2122; M-1 to L-2121; M-1 to T-2120; M-1 to P-2119; M-1 to N-2118; M-1 to T-2117; M-1 to G-2116; M-1 to E-2115; M-1 to Q-2114; M-1 to W-2113; M-1 to P-2112; M-1 to S-2111; M-1 to F-2110; M-1 to X-2109; M-1 to D-2108; M-1 to D-2107; M-1 to A-2106; M-1 to D-2105; M-1 to D-2104; M-1 to E-2103; M-1 to A-2102; M-1 to Q-2101; M-1 to F-2100; M-1 to A-2099; M-1 to S-2098; M-1 to F-2097; M-1 to G-2096; M-1 to F-2095; M-1 to G-2094; M-1 to M-2093; M-1 to P-2092; M-1 to K-2091; M-1 to G-2090; M-1 to R-2089; M-1 to A-2088; M-1 to R-2087; M-1 to L-2086; M-1 to Y-2085; M-1 to L-2084; M-1 to A-2083; M-1 to G-2082; M-1 to A-2081; M-1 to V-2080; M-1 to L-2079; M-1 to G-2078; M-1 to L-2077; M-1 to L-2076; M-1 to A-2075; M-1 to G-2074; M-1 to A-2073; M-1 to A-2072; M-1 to L-2071; M-1 to V-2070; M-1 to A-2069; M-1 to G-2068; M-1 to V-2067; M-1 to G-2066; M-1 to A-2065; M-1 to A-2064; M-1 to V-2063; M-1 to P-2062; M-1 to P-2061; M-1 to A-2060; M-1 to E-2059; M-1 to X-2058; M-1 to A-2057; M-1 to L-2056; M-1 to V-2055; M-1 to A-2054; M-1 to Q-2053; M-1 to P-2052; M-1 to Q-2051; M-1 to P-2050; M-1 to P-2049; M-1 to A-2048; M-1 to L-2047; M-1 to L-2046; M-1 to P-2045; M-1 to S-2044; M-1 to A-2043; M-1 to L-2042; M-1 to A-2041; M-1 to H-2040; M-1 to I-2039; M-1 to I-2038; M-1 to G-2037; M-1 to N-2036; M-1 to F-2035; M-1 to A-2034; M-1 to M-2033; M-1 to I-2032; M-1 to D-2031; M-1 to W-2030; M-1 to V-2029; M-1 to I-2028; M-1 to I-2027; M-1 to R-2026; M-1 to S-2025; M-1 to V-2024; M-1 to V-2023; M-1 to V-2022; M-1 to T-2021; M-1 to G-2020; M-1 to P-2019; M-1 to A-2018; M-1 to V-2017; M-1 to P-2016; M-1 to A-2015; M-1 to W-2014; M-1 to S-2013; M-1 to S-2012; M-1 to N-2011; M-1 to D-2010; M-1 to P-2009; M-1 to G-2008; M-1 to A-2007; M-1 to D-2006; M-1 to S-2005; M-1 to I-2004; M-1 to I-2003; M-1 to L-2002; M-1 to S-2001; M-1 to L-2000; M-1 to G-1999; M-1 to S-1998; M-1 to H-1997; M-1 to A-1996; M-1 to P-1995; M-1 to L-1994; M-1 to L-1993; M-1 to K-1992; M-1 to G-1991; M-1 to Q-1990; M-1 to S-1989; M-1 to A-1988; M-1 to N-1987; M-1 to A-1986; M-1 to S-1985; M-1 to L-1984; M-1 to L-1983; M-1 to T-1982; M-1 to A-1981; M-1 to N-1980; M-1 to S-1979; M-1 to A-1978; M-1 to H-1977; M-1 to L-1976; M-1 to E-1975; M-1 to L-1974; M-1 to N-1973;

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In one embodiment, the present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of the WF-HABP polypeptide depicted in Figures 2A-B (SEQ ID NO:5) or encoded by the cDNA of the



deposited clone. Particularly, in one embodiment, N-terminal deletions of the WF-HABP polypeptide can be described by the general formula m to 457, where m is an integer from 1 to 456 corresponding to the position of amino acids identified in SEQ ID NO:5 and preferably, corresponds to one of the N-terminal amino acid residues identified in the N-terminal deletions specified herein. In specific embodiments, N-terminal deletions of the WF-HABP polypeptide of the invention comprise, or alternatively, consist of, amino acid residues: N-terminal deletions of the WF-HABP polypeptide of the invention shown as SEQ ID NO:5 include polypeptides comprising the amino acid sequence of residues: V-2 to K-457; T-3 to K-457; C-4 to K-457; T-5 to K-457; C-6 to K-457; L-7 to K-457; P-8 to K-457; D-9 to K-457; Y-10 to K-457; E-11 to K-457; G-12 to K-457; D-13 to K-457; G-14 to K-457; W-15 to K-457; S-16 to K-457; C-17 to K-457; R-18 to K-457; A-19 to K-457; R-20 to K-457; N-21 to K-457; P-22 to K-457; C-23 to K-457; T-24 to K-457; D-25 to K-457; G-26 to K-457; H-27 to K-457; R-28 to K-457; G-29 to K-457; G-30 to K-457; C-31 to K-457; S-32 to K-457; E-33 to K-457; H-34 to K-457; A-35 to K-457; N-36 to K-457; C-37 to K-457; L-38 to K-457; S-39 to K-457; T-40 to K-457; G-41 to K-457; L-42 to K-457; N-43 to K-457; T-44 to K-457; R-45 to K-457; R-46 to K-457; C-47 to K-457; E-48 to K-457; C-49 to K-457; H-50 to K-457; A-51 to K-457; G-52 to K-457; Y-53 to K-457; V-54 to K-457; G-55 to K-457; D-56 to K-457; G-57 to K-457; L-58 to K-457; Q-59 to K-457; C-60 to K-457; L-61 to K-457; E-62 to K-457; E-63 to K-457; S-64 to K-457; E-65 to K-457; P-66 to K-457; P-67 to K-457; V-68 to K-457; D-69 to K-457; R-70 to K-457; C-71 to K-457; L-72 to K-457; G-73 to K-457; Q-74 to K-457; P-75 to K-457; P-76 to K-457; P-77 to K-457; C-78 to K-457; H-79 to K-457; S-80 to K-457; D-81 to K-457; A-82 to K-457; M-83 to K-457; C-84 to K-457; T-85 to K-457; D-86 to K-457; L-87 to K-457; H-88 to K-457; F-89 to K-457; Q-90 to K-457; E-91 to K-457; K-92 to K-457; R-93 to K-457; A-94 to K-457; G-95 to K-457; V-96 to K-457; F-97 to K-457; H-98 to K-457; L-99 to K-457; Q-100 to K-457; A-101 to K-457; T-102 to K-457; S-103 to K-457; G-104 to K-457; P-105 to K-457; Y-106 to K-457; G-107 to K-457; L-108 to K-457; N-109 to K-457; F-110 to K-457; S-111 to K-457; E-112 to K-457; A-113 to K-457; E-114 to K-457; A-115 to K-457; A-116 to K-457; C-117 to K-457; E-118 to K-457; A-119 to K-457; Q-120 to K-457; G-121 to K-457; A-122 to K-457; V-123 to K-457; L-124 to K-457; A-125 to K-457; S-126 to K-457; F-127 to K-457; P-128 to K-457; Q-129 to K-457; L-130 to K-457; S-131 to K-457; A-132 to K-457; A-133 to K-457; Q-134 to K-457; Q-135 to K-457; L-136 to K-457; G-137 to K-457; F-138 to K-457; H-139 to K-457; L-140 to K-457; C-141 to K-457; L-142 to K-457; M-143 to K-457; G-144 to K-457; W-145 to K-457; L-146 to K-

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30 304 to K-457; S-305 to K-457; D-306 to K-457; A-307 to K-457; G-308 to K-457; P-309 to K-457; D-310 to K-457; N-311 to K-457; S-312 to K-457; S-313 to K-457; W-314 to K-457; A-315 to K-457; P-316 to K-457; V-317 to K-457; A-318 to K-457; P-319 to K-457; G-320 to K-457; T-321 to K-457; V-322 to K-457; V-323 to K-457; V-324 to K-457; S-325 to K-

457; R-326 to K-457; I-327 to K-457; I-328 to K-457; V-329 to K-457; W-330 to K-457; D-331 to K-457; I-332 to K-457; M-333 to K-457; A-334 to K-457; F-335 to K-457; N-336 to K-457; G-337 to K-457; I-338 to K-457; I-339 to K-457; H-340 to K-457; A-341 to K-457; L-342 to K-457; A-343 to K-457; S-344 to K-457; P-345 to K-457; L-346 to K-457; L-347 to K-457; A-348 to K-457; P-349 to K-457; P-350 to K-457; Q-351 to K-457; P-352 to K-457; Q-353 to K-457; A-354 to K-457; V-355 to K-457; L-356 to K-457; A-357 to K-457; X-358 to K-457; E-359 to K-457; A-360 to K-457; P-361 to K-457; P-362 to K-457; V-363 to K-457; A-364 to K-457; A-365 to K-457; G-366 to K-457; V-367 to K-457; G-368 to K-457; A-369 to K-457; V-370 to K-457; L-371 to K-457; A-372 to K-457; A-373 to K-457; G-374 to K-457; A-375 to K-457; L-376 to K-457; L-377 to K-457; G-378 to K-457; L-379 to K-457; V-380 to K-457; A-381 to K-457; G-382 to K-457; A-383 to K-457; L-384 to K-457; Y-385 to K-457; L-386 to K-457; R-387 to K-457; A-388 to K-457; R-389 to K-457; G-390 to K-457; K-391 to K-457; P-392 to K-457; M-393 to K-457; G-394 to K-457; F-395 to K-457; G-396 to K-457; F-397 to K-457; S-398 to K-457; A-399 to K-457; F-400 to K-457; Q-401 to K-457; A-402 to K-457; E-403 to K-457; D-404 to K-457; D-405 to K-457; A-406 to K-457; D-407 to K-457; D-408 to K-457; X-409 to K-457; F-410 to K-457; S-411 to K-457; P-412 to K-457; W-413 to K-457; Q-414 to K-457; E-415 to K-457; G-416 to K-457; T-417 to K-457; N-418 to K-457; P-419 to K-457; T-420 to K-457; L-421 to K-457; V-422 to K-457; X-423 to K-457; V-424 to K-457; P-425 to K-457; N-426 to K-457; P-427 to K-457; V-428 to K-457; F-429 to K-457; G-430 to K-457; S-431 to K-457; D-432 to K-457; T-433 to K-457; F-434 to K-457; C-435 to K-457; E-436 to K-457; P-437 to K-457; F-438 to K-457; D-439 to K-457; D-440 to K-457; S-441 to K-457; L-442 to K-457; L-443 to K-457; E-444 to K-457; E-445 to K-457; D-446 to K-457; F-447 to K-457; P-448 to K-457; D-449 to K-457; T-450 to K-457; Q-451 to K-457; R-452 to K-457; of SEQ ID NO:5. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Further embodiments of the invention are directed to C-terminal deletions of the WF-HABP polypeptide described by the general formula 1 to n, where n is an integer from 2-457 corresponding to the position of amino acid residue identified in SEQ ID NO:5 and preferably, corresponds to one of the C-terminal amino acid residues identified in the C-terminal deletions specified herein. In specific embodiments, C terminal deletions of the WF-HABP polypeptide of the invention comprise, or alternatively, consist of, amino acid residues: M-1 to V-456; M-1 to T-455; M-1 to L-454; M-1 to I-453; M-1 to R-452; M-1 to Q-451; M-1 to T-450; M-1 to D-449; M-1 to P-448; M-1 to F-447; M-1 to D-446; M-1 to E-445; M-1 to E-444; M-1 to L-443;

M-1 to L-442; M-1 to S-441; M-1 to D-440; M-1 to D-439; M-1 to F-438; M-1 to P-437; M-1  
 to E-436; M-1 to C-435; M-1 to F-434; M-1 to T-433; M-1 to D-432; M-1 to S-431; M-1 to G-  
 430; M-1 to F-429; M-1 to V-428; M-1 to P-427; M-1 to N-426; M-1 to P-425; M-1 to V-424;  
 M-1 to X-423; M-1 to V-422; M-1 to L-421; M-1 to T-420; M-1 to P-419; M-1 to N-418; M-1  
 5 to T-417; M-1 to G-416; M-1 to E-415; M-1 to Q-414; M-1 to W-413; M-1 to P-412; M-1 to S-  
 411; M-1 to F-410; M-1 to X-409; M-1 to D-408; M-1 to D-407; M-1 to A-406; M-1 to D-405;  
 M-1 to D-404; M-1 to E-403; M-1 to A-402; M-1 to Q-401; M-1 to F-400; M-1 to A-399; M-1  
 to S-398; M-1 to F-397; M-1 to G-396; M-1 to F-395; M-1 to G-394; M-1 to M-393; M-1 to P-  
 392; M-1 to K-391; M-1 to G-390; M-1 to R-389; M-1 to A-388; M-1 to R-387; M-1 to L-386;  
 10 M-1 to Y-385; M-1 to L-384; M-1 to A-383; M-1 to G-382; M-1 to A-381; M-1 to V-380; M-1  
 to L-379; M-1 to G-378; M-1 to L-377; M-1 to L-376; M-1 to A-375; M-1 to G-374; M-1 to A-  
 373; M-1 to A-372; M-1 to L-371; M-1 to V-370; M-1 to A-369; M-1 to G-368; M-1 to V-367;  
 M-1 to G-366; M-1 to A-365; M-1 to A-364; M-1 to V-363; M-1 to P-362; M-1 to P-361; M-1  
 to A-360; M-1 to E-359; M-1 to X-358; M-1 to A-357; M-1 to L-356; M-1 to V-355; M-1 to A-  
 15 354; M-1 to Q-353; M-1 to P-352; M-1 to Q-351; M-1 to P-350; M-1 to P-349; M-1 to A-348;  
 M-1 to L-347; M-1 to L-346; M-1 to P-345; M-1 to S-344; M-1 to A-343; M-1 to L-342; M-1  
 to A-341; M-1 to H-340; M-1 to I-339; M-1 to I-338; M-1 to G-337; M-1 to N-336; M-1 to F-  
 335; M-1 to A-334; M-1 to M-333; M-1 to I-332; M-1 to D-331; M-1 to W-330; M-1 to V-329;  
 M-1 to I-328; M-1 to I-327; M-1 to R-326; M-1 to S-325; M-1 to V-324; M-1 to V-323; M-1 to  
 20 V-322; M-1 to T-321; M-1 to G-320; M-1 to P-319; M-1 to A-318; M-1 to V-317; M-1 to P-  
 316; M-1 to A-315; M-1 to W-314; M-1 to S-313; M-1 to S-312; M-1 to N-311; M-1 to D-310;  
 M-1 to P-309; M-1 to G-308; M-1 to A-307; M-1 to D-306; M-1 to S-305; M-1 to I-304; M-1  
 to I-303; M-1 to L-302; M-1 to S-301; M-1 to L-300; M-1 to G-299; M-1 to S-298; M-1 to H-  
 297; M-1 to A-296; M-1 to P-295; M-1 to L-294; M-1 to L-293; M-1 to K-292; M-1 to G-291;  
 25 M-1 to Q-290; M-1 to S-289; M-1 to A-288; M-1 to N-287; M-1 to A-286; M-1 to S-285; M-1  
 to L-284; M-1 to L-283; M-1 to T-282; M-1 to A-281; M-1 to N-280; M-1 to S-279; M-1 to A-  
 278; M-1 to H-277; M-1 to L-276; M-1 to E-275; M-1 to L-274; M-1 to N-273; M-1 to P-272;  
 M-1 to G-271; M-1 to S-270; M-1 to L-269; M-1 to T-268; M-1 to M-267; M-1 to N-266; M-1  
 to D-265; M-1 to V-264; M-1 to F-263; M-1 to G-262; M-1 to E-261; M-1 to N-260; M-1 to V-  
 30 259; M-1 to P-258; M-1 to V-257; M-1 to F-256; M-1 to L-255; M-1 to T-254; M-1 to K-253;  
 M-1 to Y-252; M-1 to T-251; M-1 to L-250; M-1 to E-249; M-1 to D-248; M-1 to D-247; M-1  
 to L-246; M-1 to F-245; M-1 to D-244; M-1 to L-243; M-1 to F-242; M-1 to D-241; M-1 to L-  
 240; M-1 to G-239; M-1 to R-238; M-1 to Q-237; M-1 to T-236; M-1 to A-235; M-1 to N-234;

M-1 to A-233; M-1 to Y-232; M-1 to G-231; M-1 to L-230; M-1 to L-229; M-1 to M-228; M-1  
 to G-227; M-1 to Y-226; M-1 to F-225; M-1 to T-224; M-1 to S-223; M-1 to F-222; M-1 to N-  
 221; M-1 to A-220; M-1 to T-219; M-1 to A-218; M-1 to A-217; M-1 to L-216; M-1 to V-215;  
 5 M-1 to D-214; M-1 to L-213; M-1 to L-212; M-1 to K-211; M-1 to G-210; M-1 to N-209; M-1  
 to C-208; M-1 to T-207; M-1 to S-206; M-1 to I-205; M-1 to G-204; M-1 to D-203; M-1 to G-  
 202; M-1 to V-201; M-1 to F-200; M-1 to G-199; M-1 to N-198; M-1 to R-197; M-1 to C-196;  
 M-1 to R-195; M-1 to C-194; M-1 to A-193; M-1 to V-192; M-1 to D-191; M-1 to Q-190; M-1  
 to V-189; M-1 to R-188; M-1 to F-187; M-1 to C-186; M-1 to Y-185; M-1 to A-184; M-1 to D-  
 183; M-1 to W-182; M-1 to R-181; M-1 to E-180; M-1 to S-179; M-1 to L-178; M-1 to N-177;  
 10 M-1 to K-176; M-1 to R-175; M-1 to A-174; M-1 to G-173; M-1 to L-172; M-1 to S-171; M-1  
 to V-170; M-1 to I-169; M-1 to G-168; M-1 to V-167; M-1 to R-166; M-1 to G-165; M-1 to N-  
 164; M-1 to G-163; M-1 to C-162; M-1 to D-161; M-1 to A-160; M-1 to V-159; M-1 to P-158;  
 M-1 to F-157; M-1 to V-156; M-1 to V-155; M-1 to P-154; M-1 to H-153; M-1 to A-152; M-1  
 to T-151; M-1 to S-150; M-1 to G-149; M-1 to N-148; M-1 to A-147; M-1 to L-146; M-1 to  
 15 W-145; M-1 to G-144; M-1 to M-143; M-1 to L-142; M-1 to C-141; M-1 to L-140; M-1 to H-  
 139; M-1 to F-138; M-1 to G-137; M-1 to L-136; M-1 to Q-135; M-1 to Q-134; M-1 to A-133;  
 M-1 to A-132; M-1 to S-131; M-1 to L-130; M-1 to Q-129; M-1 to P-128; M-1 to F-127; M-1  
 to S-126; M-1 to A-125; M-1 to L-124; M-1 to V-123; M-1 to A-122; M-1 to G-121; M-1 to Q-  
 120; M-1 to A-119; M-1 to E-118; M-1 to C-117; M-1 to A-116; M-1 to A-115; M-1 to E-114;  
 20 M-1 to A-113; M-1 to E-112; M-1 to S-111; M-1 to F-110; M-1 to N-109; M-1 to L-108; M-1  
 to G-107; M-1 to Y-106; M-1 to P-105; M-1 to G-104; M-1 to S-103; M-1 to T-102; M-1 to A-  
 101; M-1 to Q-100; M-1 to L-99; M-1 to H-98; M-1 to F-97; M-1 to V-96; M-1 to G-95; M-1  
 to A-94; M-1 to R-93; M-1 to K-92; M-1 to E-91; M-1 to Q-90; M-1 to F-89; M-1 to H-88; M-  
 1 to L-87; M-1 to D-86; M-1 to T-85; M-1 to C-84; M-1 to M-83; M-1 to A-82; M-1 to D-81;  
 25 M-1 to S-80; M-1 to H-79; M-1 to C-78; M-1 to P-77; M-1 to P-76; M-1 to P-75; M-1 to Q-74;  
 M-1 to G-73; M-1 to L-72; M-1 to C-71; M-1 to R-70; M-1 to D-69; M-1 to V-68; M-1 to P-  
 67; M-1 to P-66; M-1 to E-65; M-1 to S-64; M-1 to E-63; M-1 to E-62; M-1 to L-61; M-1 to C-  
 60; M-1 to Q-59; M-1 to L-58; M-1 to G-57; M-1 to D-56; M-1 to G-55; M-1 to V-54; M-1 to  
 Y-53; M-1 to G-52; M-1 to A-51; M-1 to H-50; M-1 to C-49; M-1 to E-48; M-1 to C-47; M-1  
 30 to R-46; M-1 to R-45; M-1 to T-44; M-1 to N-43; M-1 to L-42; M-1 to G-41; M-1 to T-40; M-  
 1 to S-39; M-1 to L-38; M-1 to C-37; M-1 to N-36; M-1 to A-35; M-1 to H-34; M-1 to E-33;  
 M-1 to S-32; M-1 to C-31; M-1 to G-30; M-1 to G-29; M-1 to R-28; M-1 to H-27; M-1 to G-  
 26; M-1 to D-25; M-1 to T-24; M-1 to C-23; M-1 to P-22; M-1 to N-21; M-1 to R-20; M-1 to

A-19; M-1 to R-18; M-1 to C-17; M-1 to S-16; M-1 to W-15; M-1 to G-14; M-1 to D-13; M-1 to G-12; M-1 to E-11; M-1 to Y-10; M-1 to D-9; M-1 to P-8; M-1 to L-7; of SEQ ID NO:5. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In one embodiment, the present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of the OE-HABP polypeptide depicted in Figures 3A-B (SEQ ID NO:8) or encoded by the cDNA of the deposited clone. Particularly, in one embodiment, N-terminal deletions of the OE-HABP polypeptide can be described by the general formula m to 289, where m is an integer from 1 to 288 corresponding to the position of amino acids identified in SEQ ID NO:8 and preferably, corresponds to one of the N-terminal amino acid residues identified in the N-terminal deletions specified herein. In specific embodiments, N-terminal deletions of the OE-HABP polypeptide of the invention comprise, or alternatively, consist of, amino acid residues: G-2 to K-289; L-3 to K-289; L-4 to K-289; L-5 to K-289; L-6 to K-289; V-7 to K-289; P-8 to K-289; L-9 to K-289; L-10 to K-289; L-11 to K-289; L-12 to K-289; P-13 to K-289; G-14 to K-289; S-15 to K-289; Y-16 to K-289; G-17 to K-289; L-18 to K-289; P-19 to K-289; F-20 to K-289; Y-21 to K-289; Y-22 to K-289; G-23 to K-289; F-24 to K-289; Y-25 to K-289; Y-26 to K-289; S-27 to K-289; N-28 to K-289; S-29 to K-289; A-30 to K-289; N-31 to K-289; D-32 to K-289; Q-33 to K-289; N-34 to K-289; L-35 to K-289; G-36 to K-289; N-37 to K-289; G-38 to K-289; H-39 to K-289; G-40 to K-289; K-41 to K-289; D-42 to K-289; L-43 to K-289; X-44 to K-289; N-45 to K-289; G-46 to K-289; V-47 to K-289; K-48 to K-289; L-49 to K-289; V-50 to K-289; V-51 to K-289; E-52 to K-289; T-53 to K-289; P-54 to K-289; E-55 to K-289; E-56 to K-289; T-57 to K-289; L-58 to K-289; F-59 to K-289; T-60 to K-289; Y-61 to K-289; Q-62 to K-289; G-63 to K-289; A-64 to K-289; S-65 to K-289; V-66 to K-289; I-67 to K-289; L-68 to K-289; P-69 to K-289; C-70 to K-289; R-71 to K-289; Y-72 to K-289; R-73 to K-289; Y-74 to K-289; E-75 to K-289; P-76 to K-289; A-77 to K-289; L-78 to K-289; V-79 to K-289; S-80 to K-289; P-81 to K-289; R-82 to K-289; R-83 to K-289; V-84 to K-289; R-85 to K-289; V-86 to K-289; K-87 to K-289; W-88 to K-289; W-89 to K-289; K-90 to K-289; L-91 to K-289; S-92 to K-289; E-93 to K-289; N-94 to K-289; G-95 to K-289; A-96 to K-289; P-97 to K-289; E-98 to K-289; K-99 to K-289; D-100 to K-289; V-101 to K-289; L-102 to K-289; V-103 to K-289; A-104 to K-289; I-105 to K-289; G-106 to K-289; L-107 to K-289; R-108 to K-289; H-109 to K-289; R-110 to K-289; S-111 to K-289; F-112 to K-289; G-113 to K-289; D-114 to K-289; Y-115 to K-289; Q-116 to K-289; G-117 to K-289; R-118 to K-289; V-119 to K-289; H-120 to K-289; L-121 to K-289; R-122 to K-289; Q-123 to K-289; D-124 to K-

289; K-125 to K-289; E-126 to K-289; H-127 to K-289; D-128 to K-289; V-129 to K-289; S-130 to K-289; X-131 to K-289; E-132 to K-289; I-133 to K-289; Q-134 to K-289; X-135 to K-289; L-136 to K-289; R-137 to K-289; L-138 to K-289; E-139 to K-289; D-140 to K-289; Y-141 to K-289; G-142 to K-289; R-143 to K-289; Y-144 to K-289; R-145 to K-289; C-146 to K-289; E-147 to K-289; V-148 to K-289; X-149 to K-289; D-150 to K-289; G-151 to K-289; L-152 to K-289; E-153 to K-289; D-154 to K-289; E-155 to K-289; S-156 to K-289; G-157 to K-289; L-158 to K-289; V-159 to K-289; E-160 to K-289; L-161 to K-289; E-162 to K-289; L-163 to K-289; R-164 to K-289; G-165 to K-289; V-166 to K-289; V-167 to K-289; F-168 to K-289; P-169 to K-289; Y-170 to K-289; Q-171 to K-289; S-172 to K-289; P-173 to K-289; N-174 to K-289; G-175 to K-289; R-176 to K-289; Y-177 to K-289; Q-178 to K-289; F-179 to K-289; N-180 to K-289; F-181 to K-289; H-182 to K-289; E-183 to K-289; G-184 to K-289; Q-185 to K-289; Q-186 to K-289; V-187 to K-289; C-188 to K-289; A-189 to K-289; E-190 to K-289; Q-191 to K-289; A-192 to K-289; A-193 to K-289; V-194 to K-289; V-195 to K-289; A-196 to K-289; S-197 to K-289; F-198 to K-289; E-199 to K-289; Q-200 to K-289; L-201 to K-289; F-202 to K-289; R-203 to K-289; A-204 to K-289; W-205 to K-289; E-206 to K-289; E-207 to K-289; G-208 to K-289; L-209 to K-289; D-210 to K-289; W-211 to K-289; C-212 to K-289; N-213 to K-289; A-214 to K-289; G-215 to K-289; W-216 to K-289; L-217 to K-289; Q-218 to K-289; D-219 to K-289; A-220 to K-289; T-221 to K-289; V-222 to K-289; Q-223 to K-289; Y-224 to K-289; P-225 to K-289; I-226 to K-289; M-227 to K-289; L-228 to K-289; P-229 to K-289; R-230 to K-289; Q-231 to K-289; P-232 to K-289; C-233 to K-289; G-234 to K-289; G-235 to K-289; P-236 to K-289; D-237 to K-289; L-238 to K-289; A-239 to K-289; P-240 to K-289; G-241 to K-289; V-242 to K-289; R-243 to K-289; S-244 to K-289; Y-245 to K-289; G-246 to K-289; P-247 to K-289; R-248 to K-289; H-249 to K-289; R-250 to K-289; R-251 to K-289; L-252 to K-289; H-253 to K-289; R-254 to K-289; Y-255 to K-289; D-256 to K-289; V-257 to K-289; F-258 to K-289; C-259 to K-289; F-260 to K-289; A-261 to K-289; T-262 to K-289; A-263 to K-289; L-264 to K-289; X-265 to K-289; G-266 to K-289; R-267 to K-289; V-268 to K-289; Y-269 to K-289; Y-270 to K-289; L-271 to K-289; X-272 to K-289; H-273 to K-289; P-274 to K-289; E-275 to K-289; X-276 to K-289; L-277 to K-289; T-278 to K-289; L-279 to K-289; T-280 to K-289; X-281 to K-289; A-282 to K-289; R-283 to K-289; E-284 to K-289; of SEQ ID NO:8. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Further embodiments of the invention are directed to C-terminal deletions of the OE-HABP polypeptide described by the general formula 1 to n, where n is an integer from 2-289

corresponding to the position of amino acid residue identified in SEQ ID NO:8 and preferably, corresponds to one of the C-terminal amino acid residues identified in the C-terminal deletions specified herein. In specific embodiments, C terminal deletions of the OE-HABP polypeptide of the invention comprise, or alternatively, consist of, amino acid residues: M-1 to E-288; M-1 to Q-287; M-1 to C-286; M-1 to A-285; M-1 to E-284; M-1 to R-283; M-1 to A-282; M-1 to X-281; M-1 to T-280; M-1 to L-279; M-1 to T-278; M-1 to L-277; M-1 to X-276; M-1 to E-275; M-1 to P-274; M-1 to H-273; M-1 to X-272; M-1 to L-271; M-1 to Y-270; M-1 to Y-269; M-1 to V-268; M-1 to R-267; M-1 to G-266; M-1 to X-265; M-1 to L-264; M-1 to A-263; M-1 to T-262; M-1 to A-261; M-1 to F-260; M-1 to C-259; M-1 to F-258; M-1 to V-257; M-1 to D-256; M-1 to Y-255; M-1 to R-254; M-1 to H-253; M-1 to L-252; M-1 to R-251; M-1 to R-250; M-1 to H-249; M-1 to R-248; M-1 to P-247; M-1 to G-246; M-1 to Y-245; M-1 to S-244; M-1 to R-243; M-1 to V-242; M-1 to G-241; M-1 to P-240; M-1 to A-239; M-1 to L-238; M-1 to D-237; M-1 to P-236; M-1 to G-235; M-1 to G-234; M-1 to C-233; M-1 to P-232; M-1 to Q-231; M-1 to R-230; M-1 to P-229; M-1 to L-228; M-1 to M-227; M-1 to I-226; M-1 to P-225; M-1 to Y-224; M-1 to Q-223; M-1 to V-222; M-1 to T-221; M-1 to A-220; M-1 to D-219; M-1 to Q-218; M-1 to L-217; M-1 to W-216; M-1 to G-215; M-1 to A-214; M-1 to N-213; M-1 to C-212; M-1 to W-211; M-1 to D-210; M-1 to L-209; M-1 to G-208; M-1 to E-207; M-1 to E-206; M-1 to W-205; M-1 to A-204; M-1 to R-203; M-1 to F-202; M-1 to L-201; M-1 to Q-200; M-1 to E-199; M-1 to F-198; M-1 to S-197; M-1 to A-196; M-1 to V-195; M-1 to V-194; M-1 to A-193; M-1 to A-192; M-1 to Q-191; M-1 to E-190; M-1 to A-189; M-1 to C-188; M-1 to V-187; M-1 to Q-186; M-1 to Q-185; M-1 to G-184; M-1 to E-183; M-1 to H-182; M-1 to F-181; M-1 to N-180; M-1 to F-179; M-1 to Q-178; M-1 to Y-177; M-1 to R-176; M-1 to G-175; M-1 to N-174; M-1 to P-173; M-1 to S-172; M-1 to Q-171; M-1 to Y-170; M-1 to P-169; M-1 to F-168; M-1 to V-167; M-1 to V-166; M-1 to G-165; M-1 to R-164; M-1 to L-163; M-1 to E-162; M-1 to L-161; M-1 to E-160; M-1 to V-159; M-1 to L-158; M-1 to G-157; M-1 to S-156; M-1 to E-155; M-1 to D-154; M-1 to E-153; M-1 to L-152; M-1 to G-151; M-1 to D-150; M-1 to X-149; M-1 to V-148; M-1 to E-147; M-1 to C-146; M-1 to R-145; M-1 to Y-144; M-1 to R-143; M-1 to G-142; M-1 to Y-141; M-1 to D-140; M-1 to E-139; M-1 to L-138; M-1 to R-137; M-1 to L-136; M-1 to X-135; M-1 to Q-134; M-1 to I-133; M-1 to E-132; M-1 to X-131; M-1 to S-130; M-1 to V-129; M-1 to D-128; M-1 to H-127; M-1 to E-126; M-1 to K-125; M-1 to D-124; M-1 to Q-123; M-1 to R-122; M-1 to L-121; M-1 to H-120; M-1 to V-119; M-1 to R-118; M-1 to G-117; M-1 to Q-116; M-1 to Y-115; M-1 to D-114; M-1 to G-113; M-1 to F-112; M-1 to S-111; M-1 to R-110; M-1 to H-109; M-1 to R-108; M-1 to L-107; M-1 to G-106; M-1 to I-105;



M-1 to A-104; M-1 to V-103; M-1 to L-102; M-1 to V-101; M-1 to D-100; M-1 to K-99; M-1 to E-98; M-1 to P-97; M-1 to A-96; M-1 to G-95; M-1 to N-94; M-1 to E-93; M-1 to S-92; M-1 to L-91; M-1 to K-90; M-1 to W-89; M-1 to W-88; M-1 to K-87; M-1 to V-86; M-1 to R-85; M-1 to V-84; M-1 to R-83; M-1 to R-82; M-1 to P-81; M-1 to S-80; M-1 to V-79; M-1 to L-78; M-1 to A-77; M-1 to P-76; M-1 to E-75; M-1 to Y-74; M-1 to R-73; M-1 to Y-72; M-1 to R-71; M-1 to C-70; M-1 to P-69; M-1 to L-68; M-1 to I-67; M-1 to V-66; M-1 to S-65; M-1 to A-64; M-1 to G-63; M-1 to Q-62; M-1 to Y-61; M-1 to T-60; M-1 to F-59; M-1 to L-58; M-1 to T-57; M-1 to E-56; M-1 to E-55; M-1 to P-54; M-1 to T-53; M-1 to E-52; M-1 to V-51; M-1 to V-50; M-1 to L-49; M-1 to K-48; M-1 to V-47; M-1 to G-46; M-1 to N-45; M-1 to X-44; M-1 to L-43; M-1 to D-42; M-1 to K-41; M-1 to G-40; M-1 to H-39; M-1 to G-38; M-1 to N-37; M-1 to G-36; M-1 to L-35; M-1 to N-34; M-1 to Q-33; M-1 to D-32; M-1 to N-31; M-1 to A-30; M-1 to S-29; M-1 to N-28; M-1 to S-27; M-1 to Y-26; M-1 to Y-25; M-1 to F-24; M-1 to G-23; M-1 to Y-22; M-1 to Y-21; M-1 to F-20; M-1 to P-19; M-1 to L-18; M-1 to G-17; M-1 to Y-16; M-1 to S-15; M-1 to G-14; M-1 to P-13; M-1 to L-12; M-1 to L-11; M-1 to L-10; M-1 to L-9; M-1 to P-8; M-1 to V-7; of SEQ ID NO:8. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In one embodiment, the present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of the BM-HABP polypeptide depicted in Figures 4A-B (SEQ ID NO:11) or encoded by the cDNA of the deposited clone. Particularly, in one embodiment, N-terminal deletions of the BM-HABP polypeptide can be described by the general formula m to 353, where m is an integer from 1 to 354 corresponding to the position of amino acids identified in SEQ ID NO:11 and preferably, corresponds to one of the N-terminal amino acid residues identified in the N-terminal deletions specified herein. In specific embodiments, N-terminal deletions of the BM-HABP polypeptide of the invention comprise, or alternatively, consist of, amino acid residues: N-terminal deletions of the BM-HABP polypeptide of the invention shown as SEQ ID NO:11 include polypeptides comprising the amino acid sequence of residues: N-terminal deletions of the BM-HABP polypeptide of the invention shown as SEQ ID NO:11 include polypeptides comprising the amino acid sequence of residues: N-terminal deletions of the BM-HABP polypeptide of the invention shown as SEQ ID NO:11 include polypeptides comprising the amino acid sequence of residues: T-2 to F-353; G-3 to F-353; P-4 to F-353; G-5 to F-353; K-6 to F-353; H-7 to F-353; K-8 to F-353; C-9 to F-353; E-10 to F-353; C-11 to F-353; K-12 to F-353; S-13 to F-353; H-14 to F-353; Y-15 to F-353; V-16 to F-353; G-17 to F-353; D-18 to F-353; G-19 to F-

353; L-20 to F-353; N-21 to F-353; C-22 to F-353; E-23 to F-353; P-24 to F-353; E-25 to F-353; Q-26 to F-353; L-27 to F-353; P-28 to F-353; I-29 to F-353; D-30 to F-353; R-31 to F-353; C-32 to F-353; L-33 to F-353; Q-34 to F-353; D-35 to F-353; N-36 to F-353; G-37 to F-353; Q-38 to F-353; C-39 to F-353; H-40 to F-353; A-41 to F-353; D-42 to F-353; A-43 to F-353; K-44 to F-353; C-45 to F-353; V-46 to F-353; D-47 to F-353; L-48 to F-353; H-49 to F-353; F-50 to F-353; Q-51 to F-353; D-52 to F-353; T-53 to F-353; T-54 to F-353; V-55 to F-353; G-56 to F-353; V-57 to F-353; F-58 to F-353; H-59 to F-353; L-60 to F-353; R-61 to F-353; S-62 to F-353; P-63 to F-353; L-64 to F-353; G-65 to F-353; Q-66 to F-353; Y-67 to F-353; K-68 to F-353; L-69 to F-353; T-70 to F-353; F-71 to F-353; D-72 to F-353; K-73 to F-353; A-74 to F-353; R-75 to F-353; E-76 to F-353; A-77 to F-353; C-78 to F-353; A-79 to F-353; N-80 to F-353; E-81 to F-353; A-82 to F-353; A-83 to F-353; T-84 to F-353; M-85 to F-353; A-86 to F-353; T-87 to F-353; Y-88 to F-353; N-89 to F-353; Q-90 to F-353; L-91 to F-353; S-92 to F-353; Y-93 to F-353; X-94 to F-353; Q-95 to F-353; K-96 to F-353; A-97 to F-353; K-98 to F-353; Y-99 to F-353; H-100 to F-353; L-101 to F-353; C-102 to F-353; S-103 to F-353; A-104 to F-353; G-105 to F-353; W-106 to F-353; L-107 to F-353; E-108 to F-353; T-109 to F-353; G-110 to F-353; R-111 to F-353; V-112 to F-353; A-113 to F-353; Y-114 to F-353; P-115 to F-353; T-116 to F-353; A-117 to F-353; F-118 to F-353; A-119 to F-353; S-120 to F-353; Q-121 to F-353; N-122 to F-353; C-123 to F-353; G-124 to F-353; S-125 to F-353; G-126 to F-353; V-127 to F-353; V-128 to F-353; G-129 to F-353; I-130 to F-353; V-131 to F-353; D-132 to F-353; Y-133 to F-353; G-134 to F-353; P-135 to F-353; R-136 to F-353; P-137 to F-353; N-138 to F-353; K-139 to F-353; S-140 to F-353; E-141 to F-353; M-142 to F-353; W-143 to F-353; D-144 to F-353; V-145 to F-353; F-146 to F-353; C-147 to F-353; Y-148 to F-353; R-149 to F-353; M-150 to F-353; K-151 to F-353; D-152 to F-353; V-153 to F-353; N-154 to F-353; C-155 to F-353; T-156 to F-353; X-157 to F-353; K-158 to F-353; V-159 to F-353; G-160 to F-353; Y-161 to F-353; V-162 to F-353; G-163 to F-353; D-164 to F-353; G-165 to F-353; F-166 to F-353; S-167 to F-353; Y-168 to F-353; S-169 to F-353; G-170 to F-353; N-171 to F-353; L-172 to F-353; L-173 to F-353; Q-174 to F-353; V-175 to F-353; L-176 to F-353; M-177 to F-353; S-178 to F-353; F-179 to F-353; P-180 to F-353; S-181 to F-353; L-182 to F-353; T-183 to F-353; N-184 to F-353; F-185 to F-353; L-186 to F-353; T-187 to F-353; E-188 to F-353; V-189 to F-353; L-190 to F-353; A-191 to F-353; Y-192 to F-353; S-193 to F-353; N-194 to F-353; S-195 to F-353; S-196 to F-353; A-197 to F-353; R-198 to F-353; G-199 to F-353; R-200 to F-353; A-201 to F-353; F-202 to F-353; L-203 to F-353; E-204 to F-353; H-205 to F-353; L-206 to F-353; T-207 to F-353; D-208 to F-

353; L-209 to F-353; S-210 to F-353; I-211 to F-353; R-212 to F-353; G-213 to F-353; T-214 to F-353; L-215 to F-353; F-216 to F-353; V-217 to F-353; P-218 to F-353; Q-219 to F-353; N-220 to F-353; S-221 to F-353; G-222 to F-353; L-223 to F-353; G-224 to F-353; E-225 to F-353; N-226 to F-353; E-227 to F-353; T-228 to F-353; L-229 to F-353; S-230 to F-353; G-231 to F-353; R-232 to F-353; D-233 to F-353; I-234 to F-353; E-235 to F-353; H-236 to F-353; H-237 to F-353; L-238 to F-353; A-239 to F-353; N-240 to F-353; V-241 to F-353; S-242 to F-353; M-243 to F-353; F-244 to F-353; F-245 to F-353; Y-246 to F-353; N-247 to F-353; D-248 to F-353; L-249 to F-353; V-250 to F-353; N-251 to F-353; G-252 to F-353; T-253 to F-353; T-254 to F-353; L-255 to F-353; Q-256 to F-353; T-257 to F-353; R-258 to F-353; L-259 to F-353; G-260 to F-353; S-261 to F-353; K-262 to F-353; L-263 to F-353; L-264 to F-353; I-265 to F-353; T-266 to F-353; D-267 to F-353; R-268 to F-353; Q-269 to F-353; D-270 to F-353; P-271 to F-353; L-272 to F-353; H-273 to F-353; P-274 to F-353; T-275 to F-353; E-276 to F-353; T-277 to F-353; R-278 to F-353; C-279 to F-353; V-280 to F-353; D-281 to F-353; G-282 to F-353; R-283 to F-353; D-284 to F-353; T-285 to F-353; L-286 to F-353; E-287 to F-353; W-288 to F-353; D-289 to F-353; I-290 to F-353; C-291 to F-353; A-292 to F-353; S-293 to F-353; N-294 to F-353; G-295 to F-353; I-296 to F-353; T-297 to F-353; H-298 to F-353; V-299 to F-353; I-300 to F-353; S-301 to F-353; R-302 to F-353; X-303 to F-353; L-304 to F-353; K-305 to F-353; A-306 to F-353; P-307 to F-353; P-308 to F-353; A-309 to F-353; P-310 to F-353; V-311 to F-353; T-312 to F-353; L-313 to F-353; X-314 to F-353; H-315 to F-353; T-316 to F-353; G-317 to F-353; L-318 to F-353; G-319 to F-353; X-320 to F-353; G-321 to F-353; I-322 to F-353; F-323 to F-353; X-324 to F-353; X-325 to F-353; I-326 to F-353; I-327 to F-353; L-328 to F-353; V-329 to F-353; T-330 to F-353; G-331 to F-353; A-332 to F-353; V-333 to F-353; A-334 to F-353; L-335 to F-353; A-336 to F-353; A-337 to F-353; Y-338 to F-353; S-339 to F-353; Y-340 to F-353; F-341 to F-353; R-342 to F-353; I-343 to F-353; N-344 to F-353; R-345 to F-353; K-346 to F-353; T-347 to F-353; I-348 to F-353; of SEQ ID NO:11. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Further embodiments of the invention are directed to C-terminal deletions of the BM-HABP polypeptide described by the general formula 1 to n, where n is an integer from 2-353 corresponding to the position of amino acid residue identified in SEQ ID NO:11 and preferably, corresponds to one of the C-terminal amino acid residues identified in the C-terminal deletions specified herein. In specific embodiments, C terminal deletions of the BM-HABP polypeptide of the invention comprise, or alternatively, consist of, amino acid residues:

M-1 to H-352; M-1 to X-351; M-1 to F-350; M-1 to G-349; M-1 to I-348; M-1 to T-347; M-1  
 to K-346; M-1 to R-345; M-1 to N-344; M-1 to I-343; M-1 to R-342; M-1 to F-341; M-1 to Y-  
 340; M-1 to S-339; M-1 to Y-338; M-1 to A-337; M-1 to A-336; M-1 to L-335; M-1 to A-334;  
 M-1 to V-333; M-1 to A-332; M-1 to G-331; M-1 to T-330; M-1 to V-329; M-1 to L-328; M-1  
 5 to I-327; M-1 to I-326; M-1 to X-325; M-1 to X-324; M-1 to F-323; M-1 to I-322; M-1 to G-  
 321; M-1 to X-320; M-1 to G-319; M-1 to L-318; M-1 to G-317; M-1 to T-316; M-1 to H-315;  
 M-1 to X-314; M-1 to L-313; M-1 to T-312; M-1 to V-311; M-1 to P-310; M-1 to A-309; M-1  
 to P-308; M-1 to P-307; M-1 to A-306; M-1 to K-305; M-1 to L-304; M-1 to X-303; M-1 to R-  
 302; M-1 to S-301; M-1 to I-300; M-1 to V-299; M-1 to H-298; M-1 to T-297; M-1 to I-296;  
 10 M-1 to G-295; M-1 to N-294; M-1 to S-293; M-1 to A-292; M-1 to C-291; M-1 to I-290; M-1  
 to D-289; M-1 to W-288; M-1 to E-287; M-1 to L-286; M-1 to T-285; M-1 to D-284; M-1 to R-  
 283; M-1 to G-282; M-1 to D-281; M-1 to V-280; M-1 to C-279; M-1 to R-278; M-1 to T-277;  
 M-1 to E-276; M-1 to T-275; M-1 to P-274; M-1 to H-273; M-1 to L-272; M-1 to P-271; M-1  
 to D-270; M-1 to Q-269; M-1 to R-268; M-1 to D-267; M-1 to T-266; M-1 to I-265; M-1 to L-  
 15 264; M-1 to L-263; M-1 to K-262; M-1 to S-261; M-1 to G-260; M-1 to L-259; M-1 to R-258;  
 M-1 to T-257; M-1 to Q-256; M-1 to L-255; M-1 to T-254; M-1 to T-253; M-1 to G-252; M-1  
 to N-251; M-1 to V-250; M-1 to L-249; M-1 to D-248; M-1 to N-247; M-1 to Y-246; M-1 to F-  
 245; M-1 to F-244; M-1 to M-243; M-1 to S-242; M-1 to V-241; M-1 to N-240; M-1 to A-239;  
 M-1 to L-238; M-1 to H-237; M-1 to H-236; M-1 to E-235; M-1 to I-234; M-1 to D-233; M-1  
 20 to R-232; M-1 to G-231; M-1 to S-230; M-1 to L-229; M-1 to T-228; M-1 to E-227; M-1 to N-  
 226; M-1 to E-225; M-1 to G-224; M-1 to L-223; M-1 to G-222; M-1 to S-221; M-1 to N-220;  
 M-1 to Q-219; M-1 to P-218; M-1 to V-217; M-1 to F-216; M-1 to L-215; M-1 to T-214; M-1  
 to G-213; M-1 to R-212; M-1 to I-211; M-1 to S-210; M-1 to L-209; M-1 to D-208; M-1 to T-  
 207; M-1 to L-206; M-1 to H-205; M-1 to E-204; M-1 to L-203; M-1 to F-202; M-1 to A-201;  
 25 M-1 to R-200; M-1 to G-199; M-1 to R-198; M-1 to A-197; M-1 to S-196; M-1 to S-195; M-1  
 to N-194; M-1 to S-193; M-1 to Y-192; M-1 to A-191; M-1 to L-190; M-1 to V-189; M-1 to E-  
 188; M-1 to T-187; M-1 to L-186; M-1 to F-185; M-1 to N-184; M-1 to T-183; M-1 to L-182;  
 M-1 to S-181; M-1 to P-180; M-1 to F-179; M-1 to S-178; M-1 to M-177; M-1 to L-176; M-1  
 to V-175; M-1 to Q-174; M-1 to L-173; M-1 to L-172; M-1 to N-171; M-1 to G-170; M-1 to S-  
 30 169; M-1 to Y-168; M-1 to S-167; M-1 to F-166; M-1 to G-165; M-1 to D-164; M-1 to G-163;  
 M-1 to V-162; M-1 to Y-161; M-1 to G-160; M-1 to V-159; M-1 to K-158; M-1 to X-157; M-1  
 to T-156; M-1 to C-155; M-1 to N-154; M-1 to V-153; M-1 to D-152; M-1 to K-151; M-1 to  
 M-150; M-1 to R-149; M-1 to Y-148; M-1 to C-147; M-1 to F-146; M-1 to V-145; M-1 to D-

144; M-1 to W-143; M-1 to M-142; M-1 to E-141; M-1 to S-140; M-1 to K-139; M-1 to N-138; M-1 to P-137; M-1 to R-136; M-1 to P-135; M-1 to G-134; M-1 to Y-133; M-1 to D-132; M-1 to V-131; M-1 to I-130; M-1 to G-129; M-1 to V-128; M-1 to V-127; M-1 to G-126; M-1 to S-125; M-1 to G-124; M-1 to C-123; M-1 to N-122; M-1 to Q-121; M-1 to S-120; M-1 to A-119; M-1 to F-118; M-1 to A-117; M-1 to T-116; M-1 to P-115; M-1 to Y-114; M-1 to A-113; M-1 to V-112; M-1 to R-111; M-1 to G-110; M-1 to T-109; M-1 to E-108; M-1 to L-107; M-1 to W-106; M-1 to G-105; M-1 to A-104; M-1 to S-103; M-1 to C-102; M-1 to L-101; M-1 to H-100; M-1 to Y-99; M-1 to K-98; M-1 to A-97; M-1 to K-96; M-1 to Q-95; M-1 to X-94; M-1 to Y-93; M-1 to S-92; M-1 to L-91; M-1 to Q-90; M-1 to N-89; M-1 to Y-88; M-1 to T-87; M-1 to A-86; M-1 to M-85; M-1 to T-84; M-1 to A-83; M-1 to A-82; M-1 to E-81; M-1 to N-80; M-1 to A-79; M-1 to C-78; M-1 to A-77; M-1 to E-76; M-1 to R-75; M-1 to A-74; M-1 to K-73; M-1 to D-72; M-1 to F-71; M-1 to T-70; M-1 to L-69; M-1 to K-68; M-1 to Y-67; M-1 to Q-66; M-1 to G-65; M-1 to L-64; M-1 to P-63; M-1 to S-62; M-1 to R-61; M-1 to L-60; M-1 to H-59; M-1 to F-58; M-1 to V-57; M-1 to G-56; M-1 to V-55; M-1 to T-54; M-1 to T-53; M-1 to D-52; M-1 to Q-51; M-1 to F-50; M-1 to H-49; M-1 to L-48; M-1 to D-47; M-1 to V-46; M-1 to C-45; M-1 to K-44; M-1 to A-43; M-1 to D-42; M-1 to A-41; M-1 to H-40; M-1 to C-39; M-1 to Q-38; M-1 to G-37; M-1 to N-36; M-1 to D-35; M-1 to Q-34; M-1 to L-33; M-1 to C-32; M-1 to R-31; M-1 to D-30; M-1 to I-29; M-1 to P-28; M-1 to L-27; M-1 to Q-26; M-1 to E-25; M-1 to P-24; M-1 to E-23; M-1 to C-22; M-1 to N-21; M-1 to L-20; M-1 to G-19; M-1 to D-18; M-1 to G-17; M-1 to V-16; M-1 to Y-15; M-1 to H-14; M-1 to S-13; M-1 to K-12; M-1 to C-11; M-1 to E-10; M-1 to C-9; M-1 to K-8; M-1 to H-7; of SEQ ID NO:11. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Further embodiments of the full-length WF-HABP invention are directed to polypeptide fragments comprising, or alternatively, consisting of, amino acids described by the general formula m to n, where m and n are integers corresponding to any one of the amino acid residues specified above for these symbols, respectively.

Further embodiments of the WF-HABP invention are directed to polypeptide fragments comprising, or alternatively, consisting of, amino acids described by the general formula m to n, where m and n are integers corresponding to any one of the amino acid residues specified above for these symbols, respectively.

Further embodiments of the OE-HABP invention are directed to polypeptide fragments comprising, or alternatively, consisting of, amino acids described by the general formula m to

n, where m and n are integers corresponding to any one of the amino acid residues specified above for these symbols, respectively.

Further embodiments of the BM-HABP invention are directed to polypeptide fragments comprising, or alternatively, consisting of, amino acids described by the general formula m to  
 5 n, where m and n are integers corresponding to any one of the amino acid residues specified above for these symbols, respectively.

It will be recognized in the art that some amino acid sequences of the full-length WF-HABPs can be varied without significant effect to the structure or function of the protein. If such differences in sequence are contemplated, it should be remembered that there will be  
 10 critical areas on the protein which determine activity. Thus, the invention further includes variations of full-length WF-HABPs which show substantial full-length WF-HABP receptor activity or which include regions of full-length WF-HABP proteins such as the polypeptide portions discussed below. Such mutants include deletions, insertions, inversions, repeats, and type substitutions. As indicated above, guidance concerning which amino acid changes are  
 15 likely to be phenotypically silent can be found in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990).

It will be recognized in the art that some amino acid sequences of the WF-HABPs can be varied without significant effect to the structure or function of the protein. If such differences in sequence are contemplated, it should be remembered that there will be critical  
 20 areas on the protein which determine activity. Thus, the invention further includes variations of WF-HABPs which show substantial WF-HABP receptor activity or which include regions of WF-HABP proteins such as the polypeptide portions discussed below. Such mutants include deletions, insertions, inversions, repeats, and type substitutions. As indicated above, guidance concerning which amino acid changes are likely to be phenotypically silent can be  
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concerning which amino acid changes are likely to be phenotypically silent can be found in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990).

5 It will be recognized in the art that some amino acid sequences of the BM-HABPs can be varied without significant effect to the structure or function of the protein. If such differences in sequence are contemplated, it should be remembered that there will be critical areas on the protein which determine activity. Thus, the invention further includes variations of BM-HABPs which show substantial BM-HABP receptor activity or which include regions of BM-HABP proteins such as the polypeptide portions discussed below. Such mutants  
10 include deletions, insertions, inversions, repeats, and type substitutions. As indicated above, guidance concerning which amino acid changes are likely to be phenotypically silent can be found in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990).

Thus, the fragment, derivative or analog of the polypeptide of Figures 1A-H (SEQ ID  
15 NO:2), may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the full-length WF-HABP polypeptide is fused with another compound, such as a  
20 compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) one in which the additional amino acids are fused to the full length polypeptide, such as an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the full-length WF-HABP polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art  
25 from the teachings herein.

Thus, the fragment, derivative or analog of the polypeptide of Figures 2A-B (SEQ ID  
NO:5), or that encoded by the deposited cDNA, may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or  
30 may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the WF-HABP polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) one in which the additional amino acids are fused to the

full length polypeptide, such as an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the WF-HABP polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

5        Thus, the fragment, derivative or analog of the polypeptide of Figures 3A-B (SEQ ID NO:8), or that encoded by the deposited cDNA, may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid  
10 residues includes a substituent group, or (iii) one in which the OE-HABP polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) one in which the additional amino acids are fused to the full length polypeptide, such as an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the OE-HABP polypeptide or a  
15 proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

      Thus, the fragment, derivative or analog of the polypeptide of Figures 4A-B (SEQ ID NO:11), or that encoded by the deposited cDNA, may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or  
20 may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the BM-HABP polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) one in which the additional amino acids are fused to the  
25 full length polypeptide, such as an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the BM-HABP polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

      Of particular interest are substitutions of charged amino acids with another charged  
30 amino acid and with neutral or negatively charged amino acids. The latter results in polypeptides with reduced positive charge to improve the characteristics of the full-length WF-HABP polypeptides. The prevention of aggregation is highly desirable. Aggregation of polypeptides not only results in a loss of activity but can also be problematic when preparing



pharmaceutical formulations, because they can be immunogenic. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36:838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993)).

Of particular interest are substitutions of charged amino acids with another charged amino acid and with neutral or negatively charged amino acids. The latter results in polypeptides with reduced positive charge to improve the characteristics of the WF-HABP polypeptides. The prevention of aggregation is highly desirable. Aggregation of polypeptides not only results in a loss of activity but can also be problematic when preparing pharmaceutical formulations, because they can be immunogenic. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36:838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993)).

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The replacement of amino acids can also change the selectivity of binding to cell surface receptors. For example, Ostade et al. (Nature 361:266-268 (1993)) describes certain mutations resulting in selective binding of TNF- $\alpha$  to only one of the two known types of TNF receptors. Thus, full-length WF-HABPs of the present invention may include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation.

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As indicated, changes are preferably of a minor nature, such as conservative amino acid substitutions that do not significantly affect the folding or activity of the protein (see Table 1).

TABLE 1. Conservative Amino Acid Substitutions.

Aromatic	Phenylalanine Tryptophan Tyrosine
Hydrophobic	Leucine Isoleucine Valine
Polar	Glutamine Asparagine
Basic	Arginine Lysine

These results are in line with the findings of other studies that have shown that the use of a single, standardized questionnaire can lead to biased results (e.g., [Baker et al., 2008](#)).

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Amino acids in the full-length WF-HABP polypeptides of the present invention that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, Science 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity such as receptor binding to its ligand *in vitro*, or *in vitro* (e.g., hyaluronan or chondroitin proteoglycan sulfates). Sites that are critical for ligand-receptor binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith et al., J. Mol. Biol. 224:899-904 (1992) and de Vos et al., Science 255:306-312 (1992)).

Amino acids in the WF-HABP polypeptides of the present invention that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, Science 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity such as receptor binding to its ligand *in vitro*, or *in vitro* (e.g., hyaluronan or chondroitin proteoglycan sulfates). Sites that are critical for ligand-receptor binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith et al., J. Mol. Biol. 224:899-904 (1992) and de Vos et al., Science 255:306-312 (1992)).

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are critical for ligand-receptor binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith et al., J. Mol. Biol. 224:899-904 (1992) and de Vos et al., Science 255:306-312 (1992)).

The polypeptides of the present invention also include the polypeptide of Figures 1A-H (SEQ ID NO:2); the polypeptides of Figures 1A-H (SEQ ID NO:2) minus the N-terminal methionine; the polypeptide sequence of any of the full-length WF-HABP domains described herein; the polypeptide sequence of Figures 1A-H (SEQ ID NO:2) minus a portion, or all of, one or more of the HA-binding domain, the EGF-like Type 1 domains, the EGF-like type I domains, laminin-type EGF domains, the link protein domain, the cytochrome P-450 cysteine heme-iron ligand binding domain, prokaryotic membrane lipoprotein lipid attachment site domains of the full-length WF-HABP shown in Figures 1A-H (SEQ ID NO:2); and polypeptides which are at least 80% identical, more preferably at least 85%, 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99% identical to the polypeptides described above, and also include portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids.

The polypeptides of the present invention also include the polypeptide encoded by the deposited cDNA; the polypeptide of Figures 2A-B (SEQ ID NO:5); the polypeptides of Figures 2A-B (SEQ ID NO:5) minus the N-terminal methionine; the polypeptide sequence of any of the WF-HABP domains described herein; the polypeptide sequence of Figures 2A-B (SEQ ID NO:5) minus a portion, or all of, the HA binding motif, the EGF-like Type 2 domain, and a link domain domain WF-HABP shown in Figures 2A-B (SEQ ID NO:5); and polypeptides which are at least 80% identical, more preferably at least 85%, 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99% identical to the polypeptides described above, and also include portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids.

The polypeptides of the present invention also include the polypeptide encoded by the deposited cDNA; the polypeptide of Figures 3A-B (SEQ ID NO:8); the polypeptides of Figures 3A-B (SEQ ID NO:8) minus the N-terminal methionine; the polypeptide sequence of any of the OE-HABP domains described herein; the polypeptide sequence of Figures 3A-B (SEQ ID NO:8) minus a portion, or all of, the HA binding motif domain, and a link protein domain shown in Figures 3A-B (SEQ ID NO:8); and polypeptides which are at least 80% identical, more preferably at least 85%, 90% or 95% identical, still more preferably at least 96%, 97%,

98% or 99% identical to the polypeptides described above, and also include portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids.

The polypeptides of the present invention also include the polypeptide encoded by the deposited cDNA; the polypeptide of Figures 4A-B (SEQ ID NO:11); the polypeptides of  
 5 Figures 4A-B (SEQ ID NO:11) minus the N-terminal methionine; the polypeptide sequence of any of the BM-HABP domains described herein; the polypeptide sequence of Figures 4A-B (SEQ ID NO:11) minus a portion, or all of, the HA binding motif domain, shown in Figures 4A-B (SEQ ID NO:11); and polypeptides which are at least 80% identical, more preferably at least 85%, 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99%  
 10 identical to the polypeptides described above, and also include portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a reference amino acid sequence of a full-length WF-HABP polypeptide is intended that the amino acid sequence of the polypeptide is identical to the reference sequence except that the  
 15 polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the reference amino acid of a full-length WF-HABP receptor. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a reference amino acid sequence, up to 5% of the amino acid residues in the reference sequence may be deleted or substituted with another amino acid, or a number of amino acids up to 5% of the total amino  
 20 acid residues in the reference sequence may be inserted into the reference sequence. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a reference amino acid sequence of a WF-HABP polypeptide is intended that the amino acid sequence of the polypeptide is identical to the reference sequence except that the polypeptide  
 25 sequence may include up to five amino acid alterations per each 100 amino acids of the reference amino acid of a WF-HABP receptor. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a reference amino acid sequence, up to 5% of the amino acid residues in the reference sequence may be deleted or substituted with another  
 30 amino acid, or a number of amino acids up to 5% of the total amino acid residues in the reference sequence may be inserted into the reference sequence. These alterations of the

reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

5 By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a reference amino acid sequence of a OE-HABP polypeptide is intended that the amino acid sequence of the polypeptide is identical to the reference sequence except that the polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the reference amino acid of a OE-HABP receptor. In other words, to obtain a polypeptide having  
10 an amino acid sequence at least 95% identical to a reference amino acid sequence, up to 5% of the amino acid residues in the reference sequence may be deleted or substituted with another amino acid, or a number of amino acids up to 5% of the total amino acid residues in the reference sequence may be inserted into the reference sequence. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually  
15 among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a reference amino acid sequence of a BM-HABP polypeptide is intended that the amino acid sequence of the polypeptide is identical to the reference sequence except that the polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the reference amino acid of a BM-HABP receptor. In other words, to obtain a polypeptide having  
20 an amino acid sequence at least 95% identical to a reference amino acid sequence, up to 5% of the amino acid residues in the reference sequence may be deleted or substituted with another amino acid, or a number of amino acids up to 5% of the total amino acid residues in the reference sequence may be inserted into the reference sequence. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually  
25 among residues in the reference sequence or in one or more contiguous groups within the reference sequence.  
30

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence shown in Figures 1A-H (SEQ ID NO:2), or fragments thereof, can be determined conventionally using known

computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence shown in Figures 2A-B (SEQ ID NO:5), the amino acid sequence encoded by the deposited cDNA clone, or fragments thereof, can be determined conventionally using known computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence shown in Figures 3A-B (SEQ ID NO:8), the amino acid sequence encoded by the deposited cDNA clone, or fragments thereof, can be determined conventionally using known computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence shown in Figures 4A-B (SEQ ID NO:11), the amino acid sequence encoded by the deposited cDNA clone, or



fragments thereof, can be determined conventionally using known computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

In a specific embodiment of the full-length WF-HABP invention, the identity between a reference (query) sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, is determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter. According to this embodiment, if the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction is made to the results to take into consideration the fact that the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. A determination of whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of this embodiment. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence. For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of

the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of this embodiment.

In a specific embodiment of the WF-HABP invention, the identity between a reference (query) sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, is determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter. According to this embodiment, if the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction is made to the results to take into consideration the fact that the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. A determination of whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of this embodiment. Only residues to

the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence. For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of this embodiment.

In a specific embodiment of the OE-HABP invention, the identity between a reference (query) sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, is determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter. According to this embodiment, if the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction is made to the results to take into consideration the fact that the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject

residue, as a percent of the total bases of the query sequence. A determination of whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final

5 percent identity score is what is used for the purposes of this embodiment. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence. For example, a 90 amino acid residue subject sequence is aligned with a 100

10 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the

15 final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not

20 manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of this embodiment.

In a specific embodiment of the BM-HABP invention, the identity between a reference

25 (query) sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, is determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window

30 Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter. According to this embodiment, if the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction is made to the results to take

into consideration the fact that the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. A determination of whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of this embodiment. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence. For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of this embodiment.

The polypeptides of the present full-length WF-HABP invention have uses which include, but are not limited to, molecular weight marker on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art.

The polypeptides of the present WF-HABP invention have uses which include, but are not limited to, molecular weight marker on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art.

5 The polypeptides of the present OE-HABP invention have uses which include, but are not limited to, molecular weight marker on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art.

The polypeptides of the present BM-HABP invention have uses which include, but are not limited to, molecular weight marker on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art.

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### Detection of Disease States

Cells which express full-length WF-HABP polypeptides and which are believed to be subject to increased levels of the full-length WF-HABP ligand hyaluronan during inflammatory and immunological conditions include, for example, connective cells and tissues, white fat, endothelial cells, vascular cells, atherosclerotic plaques, human umbilical vein endothelial cells (HUVECs), and other cells or tissues of highly vascularized organs or connective tissues. In addition, Northern blots revealed high levels of expression of 9.5, 4.5, 3.0 and 2.4 Kb transcripts in the heart, placenta and lung, with lower levels found in the liver, pancreas, and skeletal muscle. The 9.5 Kb band appeared to be the predominant mRNA and was especially prominent in the placenta and the heart.. By "a cellular response to a hylauronan receptor family ligand" is intended any genotypic, phenotypic, and/or morphologic change to a cell, cell line, tissue, tissue culture or patient that is induced by a hyaluronan receptor family ligand or stimuli (e.g. cytokines, injury, or IL-1b or TNF-a induction). As indicated, such cellular responses include not only normal physiological responses to hyaluronan receptor family ligands or stimuli (e.g. cytokines, injury, or IL-1b or TNF-a induction), but also diseases associated with aberrant rheological function, water homeostasis, and aberrant cell secretion, activation, survival, proliferation, migration and differentiation.

Cells which express WF-HABP polypeptides and which are believed to be subject to increased levels of the WF-HABP ligand hyaluronan during inflammatory and immunological conditions include, for example, connective cells and tissues, white fat, endothelial cells, vascular cells, atherosclerotic plaques, human umbilical vein endothelial cells (HUVECs), and other cells or tissues of highly vascularized organs or connective tissues. In addition, Northern blots revealed high levels of expression of 9.5, 4.5, 3.0 and 2.4 Kb transcripts in the heart,

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placenta and lung, with lower levels found in the liver, pancreas, and skeletal muscle. The 9.5 Kb band appeared to be the predominant mRNA and was especially prominent in the placenta and the heart.. By "a cellular response to a hylauronan receptor family ligand" is intended any genotypic, phenotypic, and/or morphologic change to a cell, cell line, tissue, tissue culture or patient that is induced by a hyaluronan receptor family ligand or stimuli (e.g. cytokines, injury, or IL-1b or TNF-a induction). As indicated, such cellular responses include not only normal physiological responses to hyaluronan receptor family ligands or stimuli (e.g. cytokines, injury, or IL-1b or TNF-a induction), but also diseases associated with aberrant rheological function, water homeostasis, and aberrant cell secretion, activation, survival, proliferation, migration and differentiation.

Cells which express OE-HABP polypeptides and which are believed to be subject to increased levels of the OE-HABP ligand hyaluronan during inflammatory and immunological conditions include, for example connective cells and tissues, osteoblasts, skeletal cells, endothelial cells, vascular cells, atherosclerotic plaques, human umbilical vein endothelial cells (HUVECs), SMC (human saphenous vein smooth muscle cells) and other cells or tissues of highly vascularized organs, or connective and/or joint tissues, such as the synovium. In addition, Northern blots revealed high levels of expression of OE-HABP mRNA in lung, placenta, and heart, with highest expression observed in the lung as a 2.2 Kb transcript. By "a cellular response to a hylauronan receptor family ligand" is intended any genotypic, phenotypic, and/or morphologic change to a cell, cell line, tissue, tissue culture or patient that is induced by a hyaluronan receptor family ligand or stimuli (e.g. cytokines, injury, or IL-1b or TNF-a induction). As indicated, such cellular responses include not only normal physiological responses to hyaluronan receptor family ligands or stimuli (e.g. cytokines, injury, or IL-1b or TNF-a induction), but also diseases associated with aberrant rheological function, water homeostasis, and aberrant cell secretion, activation, survival, proliferation, migration and differentiation.

Cells which express BM-HABP polypeptides and which are believed to be subject to increased levels of the BM-HABP ligand hyaluronan during inflammatory and immunological conditions include, for example connective cells and tissues, bone marrow, immune and/or hematopoietic cells, hepatocytes, endothelial cells, pulmonary and cardiovascular tissues, and other cells of developing tissues. In addition, Northern blots revealed high levels of expression of BM-HABP mRNA in human fetal brain, lung, liver and kidney with a distinct 9.5 Kb mRNA transcript expressed at an elevated level in fetal liver and a low level in the lung.

By "a cellular response to a hyaluronan receptor family ligand" is intended any genotypic, phenotypic, and/or morphologic change to a cell, cell line, tissue, tissue culture or patient that is induced by a hyaluronan receptor family ligand or stimuli (e.g. cytokines, injury, or IL-1b or TNF-a induction). As indicated, such cellular responses include not only normal physiological responses to hyaluronan receptor family ligands or stimuli (e.g. cytokines, injury, or IL-1b or TNF-a induction), but also diseases associated with aberrant rheological function, water homeostasis, and aberrant cell secretion, activation, survival, proliferation, migration and differentiation.

Thus, it is believed that certain tissues in mammals with certain diseases (e.g., vascular conditions, diseases associated with increased or decreased cell survival, secretion, activation, migration, differentiation, and proliferation; inflammatory diseases; ischemia; aberrant host defense; aberrant immune surveillance; arthritis; autoimmunity; (e.g., lupus erythematosus (SLE), rheumatoid arthritis (RA), insulin-dependent diabetes, multiple sclerosis (MS), giant cell arteritis, polyarteritis nodosa, myasthenia gravis, scleroderma, and graft versus host disease): immune dysfunction; and allergy), express significantly altered (e.g., enhanced or decreased) levels of the full-length WF-HABP polypeptide and mRNA encoding the full-length WF-HABP polypeptide when compared to a corresponding "standard" mammal, i.e., a mammal of the same species not having the disease. Diseases associated with increased cell survival, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors); autoimmune disorders (such as systemic lupus erythematosus and immune-related glomerulonephritis rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), information graft v. host disease, acute graft rejection, and chronic graft rejection. Diseases associated with decreased cell survival, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration); myelodysplastic syndromes (such as aplastic anemia), ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Thus, it is believed that certain tissues in mammals with certain diseases (e.g., vascular conditions, diseases associated with increased or decreased cell survival, secretion, activation, migration, differentiation, and proliferation; inflammatory diseases; ischemia; aberrant host defense; aberrant immune surveillance; arthritis; autoimmunity; (e.g., lupus erythematosus (SLE), rheumatoid arthritis (RA), insulin-dependent diabetes, multiple sclerosis (MS), giant



cell arteritis, polyarteritis nodosa, myasthenia gravis, scleroderma, and graft versus host disease): immune dysfunction; and allergy), express significantly altered (e.g., enhanced or decreased) levels of the WF-HABP polypeptide and mRNA encoding the WF-HABP polypeptide when compared to a corresponding "standard" mammal, i.e., a mammal of the same species not having the disease. Diseases associated with increased cell survival, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors); autoimmune disorders (such as systemic lupus erythematosus and immune-related glomerulonephritis rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), information graft v. host disease, acute graft rejection, and chronic graft rejection. Diseases associated with decreased cell survival, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration); myelodysplastic syndromes (such as aplastic anemia), ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Thus, it is believed that certain tissues in mammals with certain diseases (e.g., vascular conditions, diseases associated with increased or decreased cell survival, secretion, activation, migration, differentiation, and proliferation; inflammatory diseases; ischemia; aberrant host defense; aberrant immune surveillance; arthritis; autoimmunity; (e.g., lupus erythematosus (SLE), rheumatoid arthritis (RA), insulin-dependent diabetes, multiple sclerosis (MS), giant cell arteritis, polyarteritis nodosa, myasthenia gravis, scleroderma, and graft versus host disease): immune dysfunction; and allergy), express significantly altered (e.g., enhanced or decreased) levels of the OE-HABP polypeptide and mRNA encoding the OE-HABP polypeptide when compared to a corresponding "standard" mammal, i.e., a mammal of the same species not having the disease. Diseases associated with increased cell survival, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors); autoimmune disorders (such as systemic lupus erythematosus and immune-related glomerulonephritis rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), information graft v. host disease, acute graft rejection, and chronic graft rejection. Diseases associated with decreased cell survival, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration); myelodysplastic syndromes (such as aplastic anemia), ischemic injury (such as that caused by myocardial infarction, stroke

and reperfusion injury), toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Thus, it is believed that certain tissues in mammals with certain diseases (e.g., vascular conditions, diseases associated with increased or decreased cell survival, secretion, activation, migration, differentiation, and proliferation; inflammatory diseases; ischemia; aberrant host defense; aberrant immune surveillance; arthritis; autoimmunity; (e.g., lupus erythematosus (SLE), rheumatoid arthritis (RA), insulin-dependent diabetes, multiple sclerosis (MS), giant cell arteritis, polyarteritis nodosa, myasthenia gravis, scleroderma, and graft versus host disease); immune dysfunction; and allergy), express significantly altered (e.g., enhanced or decreased) levels of the BM-HABP polypeptide and mRNA encoding the BM-HABP polypeptide when compared to a corresponding "standard" mammal, i.e., a mammal of the same species not having the disease. Diseases associated with increased cell survival, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors); autoimmune disorders (such as systemic lupus erythematosus and immune-related glomerulonephritis rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), information graft v. host disease, acute graft rejection, and chronic graft rejection. Diseases associated with decreased cell survival, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration); myelodysplastic syndromes (such as aplastic anemia), ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Further, it is believed that altered levels of the full-length WF-HABP polypeptide can be detected in certain body fluids (e.g., sera, plasma, urine, synovial fluid, bronchoalveolar lavage, and spinal fluid) from mammals with the disorder when compared to sera from mammals of the same species not having the disorder. Thus, the invention provides a diagnostic method useful during diagnosis, which involves assaying the expression level of the gene encoding the full-length WF-HABP polypeptide in mammalian cells or body fluid and comparing the gene expression level with a standard full-length WF-HABP gene expression level, whereby an increase or decrease in the gene expression level over the standard is indicative of the disease.

Further, it is believed that altered levels of the WF-HABP polypeptide can be detected in certain body fluids (e.g., sera, plasma, urine, synovial fluid, bronchoalveolar lavage, and

spinal fluid) from mammals with the disorder when compared to sera from mammals of the same species not having the disorder. Thus, the invention provides a diagnostic method useful during diagnosis, which involves assaying the expression level of the gene encoding the WF-HABP polypeptide in mammalian cells or body fluid and comparing the gene expression level with a standard WF-HABP gene expression level, whereby an increase or decrease in the gene expression level over the standard is indicative of the disease.

Further, it is believed that altered levels of the OE-HABP polypeptide can be detected in certain body fluids (e.g., sera, plasma, urine, synovial fluid, bronchoalveolar lavage, and spinal fluid) from mammals with the disorder when compared to sera from mammals of the same species not having the disorder. Thus, the invention provides a diagnostic method useful during diagnosis, which involves assaying the expression level of the gene encoding the OE-HABP polypeptide in mammalian cells or body fluid and comparing the gene expression level with a standard OE-HABP gene expression level, whereby an increase or decrease in the gene expression level over the standard is indicative of the disease.

Further, it is believed that altered levels of the BM-HABP polypeptide can be detected in certain body fluids (e.g., sera, plasma, urine, synovial, and spinal fluid) from mammals with the disorder when compared to sera from mammals of the same species not having the disorder. Thus, the invention provides a diagnostic method useful during diagnosis, which involves assaying the expression level of the gene encoding the BM-HABP polypeptide in mammalian cells or body fluid and comparing the gene expression level with a standard BM-HABP gene expression level, whereby an increase or decrease in the gene expression level over the standard is indicative of the disease.

By "assaying" the expression level of the gene encoding the full-length WF-HABP polypeptide" is intended qualitatively or quantitatively measuring or estimating the level of the full-length WF-HABP polypeptide or the level of the mRNA encoding the full-length WF-HABP polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute polypeptide or mRNA level) or relatively (e.g., by comparing to the full-length WF-HABP polypeptide level or mRNA level in a second biological sample). Preferably, the full-length WF-HABP protein level or mRNA level in the first biological sample is measured or estimated and compared to a standard full-length WF-HABP receptor protein level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disease state. As will be appreciated in the art, once a standard full-

length WF-HABP receptor protein level or mRNA level is known, it can be used repeatedly as a standard for comparison.

By "assaying" the expression level of the gene encoding the WF-HABP polypeptide" is intended qualitatively or quantitatively measuring or estimating the level of the WF-HABP polypeptide or the level of the mRNA encoding the WF-HABP polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute polypeptide or mRNA level) or relatively (e.g., by comparing to the WF-HABP polypeptide level or mRNA level in a second biological sample). Preferably, the WF-HABP protein level or mRNA level in the first biological sample is measured or estimated and compared to a standard WF-HABP receptor protein level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disease state. As will be appreciated in the art, once a standard WF-HABP receptor protein level or mRNA level is known, it can be used repeatedly as a standard for comparison.

By "assaying" the expression level of the gene encoding the OE-HABP polypeptide" is intended qualitatively or quantitatively measuring or estimating the level of the OE-HABP polypeptide or the level of the mRNA encoding the OE-HABP polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute polypeptide or mRNA level) or relatively (e.g., by comparing to the OE-HABP polypeptide level or mRNA level in a second biological sample). Preferably, the OE-HABP protein level or mRNA level in the first biological sample is measured or estimated and compared to a standard OE-HABP receptor protein level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disease state. As will be appreciated in the art, once a standard OE-HABP receptor protein level or mRNA level is known, it can be used repeatedly as a standard for comparison.

By "assaying" the expression level of the gene encoding the BM-HABP polypeptide" is intended qualitatively or quantitatively measuring or estimating the level of the BM-HABP polypeptide or the level of the mRNA encoding the BM-HABP polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute polypeptide or mRNA level) or relatively (e.g., by comparing to the BM-HABP polypeptide level or mRNA level in a second biological sample). Preferably, the BM-HABP protein level or mRNA level in the first biological sample is measured or estimated and compared to a standard BM-HABP receptor protein level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disease state. As will be appreciated in the art, once

a standard BM-HABP receptor protein level or mRNA level is known, it can be used repeatedly as a standard for comparison.

By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source which contains full-length WF-HABP receptor protein or mRNA. Biological samples include mammalian body fluids (such as sera, plasma, urine, lymph, pulmonary sputum or surfactant, synovial fluid and spinal fluid), and heart, placenta, lung, liver, pancreas, skeletal muscle, connective cells and tissues, white fat, endothelial cells, vascular cells, atherosclerotic plaques, human umbilical vein endothelial cells (HUVECs), and other cells or tissues of highly vascularized organs or connective tissues. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source which contains WF-HABP receptor protein or mRNA. Biological samples include mammalian body fluids (such as sera, plasma, urine, lymph, pulmonary sputum or surfactant, synovial fluid and spinal fluid), and heart, placenta, lung, liver, pancreas, skeletal muscle, connective cells and tissues, white fat, endothelial cells, vascular cells, atherosclerotic plaques, human umbilical vein endothelial cells (HUVECs), and other cells or tissues of highly vascularized organs or connective tissues. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source which contains OE-HABP receptor protein or mRNA. Biological samples include mammalian body fluids (such as sera, plasma, lymph, urine, pulmonary sputum or surfactant, synovial fluid and spinal fluid), and heart, placenta, lung, liver, pancreas, skeletal muscle, connective cells and tissues, osteoblasts, endothelial cells, vascular cells, atherosclerotic plaques, human umbilical vein endothelial cells (HUVECs), SMC (human saphenous vein smooth muscle cells), and other cells or tissues of highly vascularized organs, connective or skeletal tissues, such as the synovium. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source which contains BM-HABP receptor protein or mRNA. Biological samples include mammalian body fluids (such as sera, plasma, lymph, urine,

pulmonary sputum or surfactant, synovial fluid and spinal fluid), human fetal brain, lung, liver, kidney, connective cells and tissues, bone marrow, endothelial cells, and other cells or tissues of developmental tissues. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

Where a diagnosis has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting altered full-length WF-HABP gene expression will experience a worse clinical outcome relative to patients expressing the gene at a normal level.

Where a diagnosis has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting altered WF-HABP gene expression will experience a worse clinical outcome relative to patients expressing the gene at a normal level.

Where a diagnosis has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting altered OE-HABP gene expression will experience a worse clinical outcome relative to patients expressing the gene at a normal level.

Where a diagnosis has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting altered BM-HABP gene expression will experience a worse clinical outcome relative to patients expressing the gene at a normal level.

Nucleic acids for diagnosis may be obtained from a biological sample of a subject, such as from blood, urine, saliva, lymph, tissue biopsy or autopsy material, using techniques known in the art. The genomic DNA may be used directly for detection or may be amplified enzymatically by using PCR or other amplification techniques prior to analysis. RNA or cDNA may also be used in similar fashion. Deletions and insertions can be detected by a change in size of the amplified product in comparison to the normal genotype. Point mutations can be identified by hybridizing amplified DNA to labeled full-length WF-HABP nucleotide sequences. Perfectly matched sequences can be distinguished from mismatched duplexes by RNase digestion or by differences in melting temperatures. DNA sequence differences may also be detected by alterations in electrophoretic mobility of DNA fragments in gels, with or without denaturing agents, or by direct DNA sequencing (see, e.g., Myers et al., Science 230:1242 (1985)). Sequence changes at specific locations may also be revealed by nuclease

protection assays, such as RNase and S1 protection or the chemical cleavage method (see Cotton et al., Proc. Natl. Acad. Sci. USA 85:4397-4401 (1985)). In another embodiment, an array of oligonucleotides probes comprising full-length WF-HABP polynucleotide sequences or fragments thereof, can be constructed to conduct efficient screening of e.g., genetic mutations. Array technology methods are well known and have general applicability and can be used to address a variety of questions in molecular genetics including gene expression, genetic linkage, and genetic variability (see for example, Chee et al., Science 274:610-613 (1996)).

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The diagnostic assays offer a process for diagnosing or determining a susceptibility to specific diseases through detection of mutation in the full-length WF-HABP gene by the methods described herein or otherwise known in the art.

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In addition, specific diseases can be diagnosed by methods comprising those which derive a sample from a subject with an abnormally decreased or increased level of full-length  
 15 WF-HABP polypeptide or mRNA. Decreased or increased expression can be measured at the RNA level using any of the methods well known in the art, which include, but are not limited to, Northern blot analysis, (Harada et al., Cell 63:303-312 (1990)), S1 nuclease mapping (Fijita et al., Cell 49:357-367 (1987)), RNase protection, the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR)  
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Assaying full-length WF-HABP polypeptide levels in a biological sample can be by any techniques known in the art, which include, but are not limited to, radioimmunoassays, competitive-binding assays, Western Blot analysis and enzyme linked immunosorbent assays (ELISAs) and other antibody-based techniques. For example, full-length WF-HABP  
 20 polypeptide expression in tissues can be studied with classical immunohistological methods (Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen et al., J. Cell. Biol. 105:3087-3096 (1987)).

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Suitable labels for the full-length WF-HABP invention are known in the art and include enzyme labels, such as, Glucose oxidase, and radioisotopes, such as iodine ( $^{125}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{112}\text{In}$ ), and technetium ( $^{99\text{m}}\text{Tc}$ ), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

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## Antibodies

Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of SEQ ID NOs: 2, 5, 8, or 11, and/or an epitope, of the present invention (as determined by immunoassays well known in the art for assaying specific antibody-antigen binding). Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic

(anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule.

Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')<sub>2</sub>, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, ship rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described

herein, e.g., by N-terminal and C-terminal positions, by size in contiguous amino acid residues, or listed in the Tables and Figures. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, or  $10^{-15}$  M.

The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described supra). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., *Blood* 92(6):1981-1988 (1998); Chen et al., *Cancer Res.* 58(16):3668-3678 (1998); Harrop et al., *J. Immunol.* 161(4):1786-1794 (1998); Zhu et al., *Cancer Res.* 58(15):3209-3214 (1998); Yoon et al., *J. Immunol.* 160(7):3170-3179 (1998); Prat et al., *J. Cell. Sci.* 111(Pt2):237-247 (1998); Pitard et al., *J. Immunol. Methods* 205(2):177-190 (1997); Liautard et al., *Cytokine* 9(4):233-241 (1997); Carlson et al., *J. Biol. Chem.* 272(17):11295-11301 (1997); Taryman et al., *Neuron* 14(4):755-762 (1995); Muller et al., *Structure* 6(9):1153-1167 (1998); Bartunek

et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

Antibodies of the present invention may be used, for example, but not limited to, to purify, detect, and target the polypeptides of the present invention, including both in vitro and in vivo diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

The antibodies of the invention include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of-interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host

species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples (e.g., Example 16). In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.



Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')<sub>2</sub> fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). F(ab')<sub>2</sub> fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., *J. Immunol. Methods* 182:41-50 (1995); Ames et al., *J. Immunol. Methods* 184:177-186 (1995); Kettleborough et al., *Eur. J. Immunol.* 24:952-958 (1994); Persic et al., *Gene* 187 9-18 (1997); Burton et al., *Advances in Immunology* 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')<sub>2</sub> fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., *BioTechniques* 12(6):864-869 (1992); and

Sawai et al., AJRI 34:26-34 (1995); and Better et al., Science 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., Methods in Enzymology 203:46-88 (1991); Shu et al., PNAS 90:7995-7999 (1993); and Skerra et al., Science 240:1038-1040 (1988). For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol. Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human

immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

5 Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity  
10 region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred  
15 to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human  
20 immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, *Int. Rev. Immunol.* 13:65-93 (1995). For a detailed discussion of this  
25 technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598, which are incorporated by reference herein in their entirety. In addition,  
30 companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., *Bio/technology* 12:899-903 (1988)).

Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, *FASEB J.* 7(5):437-444; (1989) and Nissinoff, J. *Immunol.* 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand. For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligands/receptors, and thereby block its biological activity.

#### Polynucleotides Encoding Antibodies

The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NOs: 2, 5, 8, or 11.

The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., *BioTechniques* 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is

not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells  
 5 selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

10 Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring  
 15 Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, the amino acid sequence of the heavy and/or light chain  
 20 variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well known in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework  
 25 regions to humanize a non-human antibody, as described supra. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the  
 30 invention. Preferably, as discussed supra, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an

intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described supra, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423-42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in *E. coli* may also be used (Skerra et al., Science 242:1038-1041 (1988)).

## Methods of Producing Antibodies

The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression

vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the

adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in  
 5 conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., *Gene* 45:101 (1986); Cockett et al., *Bio/Technology* 8:2 (1990)).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example,  
 10 when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al., *EMBO J.* 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in  
 15 frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, *Nucleic Acids Res.* 13:3101-3109 (1985); Van Heeke & Schuster, *J. Biol. Chem.* 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to  
 20 matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The  
 25 antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of  
 30 interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and



capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines

may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., *Cell* 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, *Proc. Natl. Acad. Sci. USA* 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., *Cell* 22:817 (1980)) genes can be employed in tk-, hgp<sup>r</sup>t- or ap<sup>r</sup>t- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., *Natl. Acad. Sci. USA* 77:357 (1980); O'Hare et al., *Proc. Natl. Acad. Sci. USA* 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, *Proc. Natl. Acad. Sci. USA* 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 *Clinical Pharmacy* 12:488-505; Wu and Wu, *Biotherapy* 3:87-95 (1991); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); May, 1993, *TIB TECH* 11(5):155-215); and hyg<sup>r</sup>, which confers resistance to hygromycin (Santerre et al., *Gene* 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), *Current Protocols in Human Genetics*, John Wiley & Sons, NY (1994); Colberre-Garapin et al., *J. Mol. Biol.* 150:1 (1981), which are incorporated by reference herein in their entireties.

The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, *The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning*, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., *Mol. Cell. Biol.* 3:257 (1983)).

The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light

chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or in vivo, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., supra, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452(1991), which are incorporated by reference in their entireties.

The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated to an

antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form

5 multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851;

10 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337-11341(1992) (said references incorporated by reference in their entireties).

As discussed, supra, the polypeptides corresponding to a polypeptide, polypeptide

15 fragment, or a variant of SEQ ID NO: 2, 5, 8, or 11 may be fused or conjugated to the above antibody portions to increase the in vivo half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to SEQ ID NO: 2, 5, 8, or 11 may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first

20 two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP 394,827; Traunecker et al., Nature 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide-linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein

25 fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995)). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP A 232,262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as

30 an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., J. Molecular Recognition 8:52-58 (1995); Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).

Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{111}\text{In}$  or  $^{99}\text{Tc}$ .

Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example,  $^{213}\text{Bi}$ . A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, teniposide, vincristine, vinblastine,

colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor,  $\alpha$ -interferon,  $\beta$ -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF- $\alpha$ , TNF- $\beta$ , AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti- angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in *Controlled*

Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

### Immunophenotyping

The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. The translation product of the gene of the present invention may be useful as a cell specific marker, or more specifically as a cellular marker that is differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al.*, *Cell*, 96:737-49 (1999)).

These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

### Assays For Antibody Binding

The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich"

5 immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which  
10 is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X- 100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with  
15 protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to  
20 immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John  
25 Wiley & Sons, Inc., New York at 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking  
30 solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-



human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g.,  $^{32}\text{P}$  or  $^{125}\text{I}$ ) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g.,  $^3\text{H}$  or  $^{125}\text{I}$ ) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g.,  $^3\text{H}$  or  $^{125}\text{I}$ ) in the presence of increasing amounts of an unlabeled second antibody.

### Therapeutic Uses

The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, and  $10^{-15}$  M.

#### Gene Therapy

In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., *Clinical Pharmacy* 12:488-505 (1993); Wu and Wu, *Biotherapy* 3:87-95 (1991); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); May, *TIBTECH* 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); and Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990).

In a preferred aspect, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In

another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)). In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

In a specific embodiment, the nucleic acid sequences are directly administered in vivo, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., *Meth. Enzymol.* 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA.

5 The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., *Biotherapy* 6:291-302 (1994), which describes the use of a retroviral vector to deliver the *mdr1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the

10 use of retroviral vectors in gene therapy are: Clowes et al., *J. Clin. Invest.* 93:644-651 (1994); Kiem et al., *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993).

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are

15 especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993)

20 present a review of adenovirus-based gene therapy. Bout et al., *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., *Science* 252:431-434 (1991); Rosenfeld et al., *Cell* 68:143-155 (1992); Mastrangeli et al., *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and

25 Wang, et al., *Gene Therapy* 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., *Proc. Soc. Exp. Biol. Med.* 204:289-300 (1993); U.S. Patent No. 5,436,146).

Another approach to gene therapy involves transferring a gene to cells in tissue culture by

30 such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, *Meth. Enzymol.* 217:599-618 (1993); Cohen et al., *Meth. Enzymol.* 217:618-644 (1993); Cline, *Pharmac. Ther.* 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as Tlymphocytes, Blymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, *Cell* 71:973-985 (1992); Rheinwald, *Meth. Cell Bio.* 21A:229 (1980); and Pittelkow and Scott, *Mayo Clinic Proc.* 61:771 (1986)).

In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription. **Demonstration of Therapeutic or Prophylactic Activity**

5       The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue  
10       sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of  
15       such compound upon the tissue sample is observed.

#### Therapeutic/Prophylactic Administration and Composition

20       The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably an antibody of the invention. In a preferred aspect, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

25       Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

30       Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal,

intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other  
 5 biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can  
 10 also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery,  
 15 topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

20 In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)

In yet another embodiment, the compound or composition can be delivered in a  
 25 controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); *Controlled Drug Bioavailability, Drug*  
 30 *Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., *Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); see also Levy et al., *Science* 228:190 (1985); During et al., *Ann. Neurol.* 25:351 (1989); Howard et al., *J.Neurosurg.* 71:105 (1989)). In yet another embodiment, a controlled release system can be



placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in *Medical Applications of Controlled Release*, supra, vol. 2, pp. 115-138 (1984)).

Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see e.g., Joliot et al., *Proc. Natl. Acad. Sci. USA* 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and

carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human  
 5 body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

10 The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale  
 15 for human administration. **Diagnosis and Imaging**

Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases and/or disorders associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression  
 20 of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

25 The invention provides a diagnostic assay for diagnosing a disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is  
 30 indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow

health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine ( $^{125}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{112}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of  $^{99\text{m}}\text{Tc}$ . The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disorder, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labeled molecule can be detected in the patient using methods known in the art for in vivo scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

#### Kits

The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-

well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

## 10 Agonists and Antagonists of WF-HABP

In one embodiment, the present invention is directed to a method for identifying compounds that interact with (e.g., bind to) full-length WF-HABP polypeptides (including, but not limited to full-length WF-HABP, and one or more hyaluronan binding domains of full-length WF-HABP). Compounds identified may be useful, for example, in modulating the activity full-length WF-HABP gene products; in elaborating the biological function of full-length WF-HABP; in screens for identifying compounds that disrupt normal full-length WF-HABP interactions; or may in themselves disrupt such interactions and therefore may have uses which include, for example, regulators of hematopoiesis and/or of the immune response.

In one embodiment, the present invention is directed to a method for identifying compounds that interact with (e.g., bind to) WF-HABP polypeptides (including, but not limited to WF-HABP, and one or more hyaluronan binding domains of WF-HABP). Compounds identified may be useful, for example, in modulating the activity WF-HABP gene products; in elaborating the biological function of WF-HABP; in screens for identifying compounds that disrupt normal WF-HABP interactions; or may in themselves disrupt such interactions and therefore may have uses which include, for example, regulators of hematopoiesis and/or of the immune response.

In one embodiment, the present invention is directed to a method for identifying compounds that interact with (e.g., bind to) OE-HABP polypeptides (including, but not limited to OE -HABP, and one or more hyaluronan binding domains of OE -HABP). Compounds identified may be useful, for example, in modulating the activity OE -HABP gene products; in elaborating the biological function of OE -HABP; in screens for identifying compounds that disrupt normal OE -HABP interactions; or may in themselves disrupt such interactions and

therefore may have uses which include, for example, regulators of hematopoiesis and/or of the immune response.

In one embodiment, the present invention is directed to a method for identifying compounds that interact with (e.g., bind to) BM-HABP polypeptides (including, but not limited to BM -HABP, and one or more hyaluronan binding domains of BM -HABP). Compounds identified may be useful, for example, in modulating the activity BM -HABP gene products; in elaborating the biological function of BM -HABP; in screens for identifying compounds that disrupt normal BM -HABP interactions; or may in themselves disrupt such interactions and therefore may have uses which include, for example, regulators of hematopoiesis, and/or of the immune response.

The principle of the assays used to identify compounds that bind to full-length WF-HABP involves preparing a reaction mixture of full-length WF-HABP and the test compound under conditions and for a time sufficient to allow the two components to interact and bind, thus forming a complex which can be removed and/or detected in the reaction mixture. The full-length WF-HABP polypeptide species used can vary depending upon the goal of the screening assay. For example, where agonists of the natural ligand are sought, the full length WF-HABP, or a soluble truncated full-length WF-HABP (e.g., containing one or more binding domains (i.e. EGF-like type 1 domain, EGF-like type 2 domain, laminin-type EGF, cytochrome P450 cysteine heme-iron ligand binding domains, prokaryotic membrane lipoprotein lipid attachment site domains), a peptide corresponding to a full-length WF-HABP hyaluronan binding domain or a fusion protein containing a full-length WF-HABP hyaluronan binding domain fused to a polypeptide that affords advantages in the assay system (e.g., labeling, isolation of the resulting complex, etc.) can be utilized. Where compounds that interact with a full-length WF-HABP binding domain are sought to be identified, peptides corresponding to the full-length WF-HABP binding domain and fusion proteins containing a full-length WF-HABP binding domain can be used.

The principle of the assays used to identify compounds that bind to WF-HABP involves preparing a reaction mixture of WF-HABP and the test compound under conditions and for a time sufficient to allow the two components to interact and bind, thus forming a complex which can be removed and/or detected in the reaction mixture. The WF-HABP polypeptide species used can vary depending upon the goal of the screening assay. For example, where agonists of the natural ligand are sought, the WF-HABP, or a soluble truncated WF-HABP (e.g., containing one or more binding domains (i.e. EGF-like type 2



domain, link-protein binding domain), a peptide corresponding to a WF-HABP hyaluronan binding domain or a fusion protein containing a WF-HABP hyaluronan binding domain fused to a polypeptide that affords advantages in the assay system (e.g., labeling, isolation of the resulting complex, etc.) can be utilized. Where compounds that interact with a WF-HABP binding domain are sought to be identified, peptides corresponding to the WF-HABP binding domain and fusion proteins containing a WF-HABP binding domain can be used.

The principle of the assays used to identify compounds that bind to OE-HABP involves preparing a reaction mixture of OE-HABP and the test compound under conditions and for a time sufficient to allow the two components to interact and bind, thus forming a complex which can be removed and/or detected in the reaction mixture. The OE-HABP polypeptide species used can vary depending upon the goal of the screening assay. For example, where agonists of the natural ligand are sought, the OE-HABP, or a soluble truncated OE-HABP (e.g., containing one or more binding domains (i.e. link-protein binding domain), a peptide corresponding to a OE-HABP hyaluronan binding domain or a fusion protein containing a OE-HABP hyaluronan binding domain fused to a polypeptide that affords advantages in the assay system (e.g., labeling, isolation of the resulting complex, etc.) can be utilized. Where compounds that interact with a OE-HABP binding domain are sought to be identified, peptides corresponding to the OE-HABP binding domain and fusion proteins containing a OE-HABP binding domain can be used.

The principle of the assays used to identify compounds that bind to BM-HABP involves preparing a reaction mixture of BM-HABP and the test compound under conditions and for a time sufficient to allow the two components to interact and bind, thus forming a complex which can be removed and/or detected in the reaction mixture. The BM-HABP polypeptide species used can vary depending upon the goal of the screening assay. For example, where agonists of the natural ligand are sought, the BM-HABP, or a soluble truncated BM-HABP (e.g., containing one or more binding domains (i.e. link-protein binding domain), a peptide corresponding to a BM-HABP hyaluronan binding domain or a fusion protein containing a BM-HABP hyaluronan binding domain fused to a polypeptide that affords advantages in the assay system (e.g., labeling, isolation of the resulting complex, etc.) can be utilized. Where compounds that interact with a BM-HABP binding domain are sought to be identified, peptides corresponding to the BM-HABP binding domain and fusion proteins containing a BM-HABP binding domain can be used.

The compounds that may be screened in accordance with the invention include, but are not limited to, soluble peptides, including but not limited to those found in random peptide libraries; (see, e.g., Lam et al., *Nature* 354:82-84 (1991); Houghten, R. et al., *Nature* 354:84-86 (1991)), cell or tissue lysates, and biological samples (e.g., cells, tissue, sera and lymph).

5 Such compounds may also be found in random peptide expression libraries, and genomic or cDNA expression libraries, or combinatorial chemistry-derived molecular libraries made of D- and/or L- configuration amino acids; phosphopeptides (including, but not limited to members of random or partially degenerate, directed phosphopeptide libraries; see, e.g., Songyang et al., *Cell* 72:767-778 (1993)); antibodies (including, but not limited to, polyclonal, monoclonal, 10 humanized, anti-idiotypic, chimeric or single chain antibodies, and FAb, F(ab')<sub>2</sub> and FAb expression library fragments, and epitope-binding fragments thereof); and small organic or inorganic molecules.

Numerous experimental methods may be used to select and detect polypeptides that bind with full-length WF-HABP, including, but not limited to, protein affinity 15 chromatography, hyaluronan or proteoglycan affinity chromatography, affinity blotting, immunoprecipitation, cross-linking, and library based methods such as protein probing, phage display and the two-hybrid system. See generally, Phizicky et al., *Microbiol. Rev.* 59:94-123 (1995). Once isolated, such a full-length WF-HABP-binding polypeptide can be identified and can, in turn, be used, in conjunction with standard techniques, to identify polypeptides with 20 which it interacts. For example, at least a portion of the amino acid sequence of a polypeptide that interacts with full-length WF-HABP can be ascertained using techniques well known to those of skill in the art, such as via the Edman degradation technique. (See, e.g., Creighton, 1983, "Proteins: Structures and Molecular Principles", W.H. Freeman & Co., N.Y., pp.34-49). The amino acid sequence obtained may be used as a guide for the generation of 25 oligonucleotide mixtures that can be used to screen for gene sequences encoding such polypeptides. Screening may be accomplished, for example, by standard hybridization or PCR techniques. Techniques for the generation of oligonucleotide mixtures and the screening are well-known. (See, e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press; and *PCR Protocols: A Guide to* 30 *Methods and Applications*, 1990, Innis, M. et al., eds. Academic Press, Inc., New York).

Numerous experimental methods may be used to select and detect polypeptides that bind with WF-HABP, including, but not limited to, protein affinity chromatography, hyaluronan or proteoglycan affinity chromatography, affinity blotting, immunoprecipitation,

cross-linking, and library based methods such as protein probing, phage display and the two-hybrid system. See generally, Phizicky et al., *Microbiol. Rev.* 59:94-123 (1995). Once isolated, such a WF-HABP-binding polypeptide can be identified and can, in turn, be used, in conjunction with standard techniques, to identify polypeptides with which it interacts. For example, at least a portion of the amino acid sequence of a polypeptide that interacts with WF-HABP can be ascertained using techniques well known to those of skill in the art, such as via the Edman degradation technique. (See, e.g., Creighton, 1983, "Proteins: Structures and Molecular Principles", W.H. Freeman & Co., N.Y., pp.34-49). The amino acid sequence obtained may be used as a guide for the generation of oligonucleotide mixtures that can be used to screen for gene sequences encoding such polypeptides. Screening may be accomplished, for example, by standard hybridization or PCR techniques. Techniques for the generation of oligonucleotide mixtures and the screening are well-known. (See, e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press; and *PCR Protocols: A Guide to Methods and Applications*, 1990, Innis, M. et al., eds. Academic Press, Inc., New York).

Numerous experimental methods may be used to select and detect polypeptides that bind with OE-HABP, including, but not limited to, protein affinity chromatography, hyaluronan or proteoglycan affinity chromatography, affinity blotting, immunoprecipitation, cross-linking, and library based methods such as protein probing, phage display and the two-hybrid system. See generally, Phizicky et al., *Microbiol. Rev.* 59:94-123 (1995). Once isolated, such a OE-HABP-binding polypeptide can be identified and can, in turn, be used, in conjunction with standard techniques, to identify polypeptides with which it interacts. For example, at least a portion of the amino acid sequence of a polypeptide that interacts with OE-HABP can be ascertained using techniques well known to those of skill in the art, such as via the Edman degradation technique. (See, e.g., Creighton, 1983, "Proteins: Structures and Molecular Principles", W.H. Freeman & Co., N.Y., pp.34-49). The amino acid sequence obtained may be used as a guide for the generation of oligonucleotide mixtures that can be used to screen for gene sequences encoding such polypeptides. Screening may be accomplished, for example, by standard hybridization or PCR techniques. Techniques for the generation of oligonucleotide mixtures and the screening are well-known. (See, e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press; and *PCR Protocols: A Guide to Methods and Applications*, 1990, Innis, M. et al., eds. Academic Press, Inc., New York).

Numerous experimental methods may be used to select and detect polypeptides that bind with BM-HABP, including, but not limited to, protein affinity chromatography, hyaluronan or proteoglycan affinity chromatography, affinity blotting, immunoprecipitation, cross-linking, and library based methods such as protein probing, phage display and the two-hybrid system. See generally, Phizicky et al., *Microbiol. Rev.* 59:94-123 (1995). Once isolated, such a BM-HABP-binding polypeptide can be identified and can, in turn, be used, in conjunction with standard techniques, to identify polypeptides with which it interacts. For example, at least a portion of the amino acid sequence of a polypeptide that interacts with BM-HABP can be ascertained using techniques well known to those of skill in the art, such as via the Edman degradation technique. (See, e.g., Creighton, 1983, "Proteins: Structures and Molecular Principles", W.H. Freeman & Co., N.Y., pp.34-49). The amino acid sequence obtained may be used as a guide for the generation of oligonucleotide mixtures that can be used to screen for gene sequences encoding such polypeptides. Screening may be accomplished, for example, by standard hybridization or PCR techniques. Techniques for the generation of oligonucleotide mixtures and the screening are well-known. (See, e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press; and *PCR Protocols: A Guide to Methods and Applications*, 1990, Innis, M. et al., eds. Academic Press, Inc., New York).

Additionally, methods may be employed which result in the simultaneous identification of genes which encode polypeptides interacting with full-length WF-HABP. These methods include, for example, probing expression libraries, in a manner similar to the well known technique of antibody probing of gt11 libraries, using labeled full-length WF-HABP polypeptide, such as a full-length WF-HABP fusion protein wherein a full-length WF-HABP domain is fused to a marker (e.g., an enzyme, fluor, luminescent protein, or dye), or an Ig-Fc domain. For example, the two-hybrid system may be used to detect interaction between full-length WF-HABP and candidate proteins for which genes encoding the candidate polypeptides are available by constructing the appropriate hybrids and testing for reporter gene activity. If an interaction is detected using the two-hybrid method, deletions can be made in the DNA encoding the candidate interacting polypeptide or the full-length WF-HABP polypeptide to identify a minimal domain for interaction. Alternatively, the two-hybrid system can be used to screen available organismal and/or mammalian tissue specific libraries of activation domain hybrids to identify polypeptides that bind to a full-length WF-HABP polypeptide. These screens result in the immediate availability of the cloned gene for any new polypeptide

identified. In addition, since multiple clones that encode overlapping regions of protein are often identified, the minimal domain for interaction may be readily apparent from the initial screen.

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Additionally, methods may be employed which result in the simultaneous identification of genes which encode polypeptides interacting with OE -HABP. These methods include, for example, probing expression libraries, in a manner similar to the well known technique of antibody probing of gt11 libraries, using labeled OE -HABP polypeptide, such as a OE -HABP fusion protein wherein a OE -HABP domain is fused to a marker (e.g., an enzyme, fluor, luminescent protein, or dye), or an Ig-Fc domain. For example, the two-hybrid system may be used to detect interaction between OE -HABP and candidate proteins for which genes encoding the candidate polypeptides are available by constructing the appropriate hybrids and testing for reporter gene activity. If an interaction is detected using the two-hybrid method, deletions can be made in the DNA encoding the candidate interacting polypeptide or the OE -HABP polypeptide to identify a minimal domain for interaction. Alternatively, the two-hybrid system can be used to screen available organismal and/or mammalian tissue specific libraries of activation domain hybrids to identify polypeptides that bind to a OE-HABP polypeptide. These

screens result in the immediate availability of the cloned gene for any new polypeptide identified. In addition, since multiple clones that encode overlapping regions of protein are often identified, the minimal domain for interaction may be readily apparent from the initial screen.

5           Additionally, methods may be employed which result in the simultaneous identification of genes which encode polypeptides interacting with BM -HABP. These methods include, for example, probing expression libraries, in a manner similar to the well known technique of antibody probing of gt11 libraries, using labeled BM -HABP polypeptide, such as a BM -HABP fusion protein wherein a BM -HABP domain is fused to a marker (e.g., an enzyme, fluor, luminescent protein, or dye), or an Ig-Fc domain. For example, the two-hybrid system  
10           may be used to detect interaction between BM -HABP and candidate proteins for which genes encoding the candidate polypeptides are available by constructing the appropriate hybrids and testing for reporter gene activity. If an interaction is detected using the two-hybrid method, deletions can be made in the DNA encoding the candidate interacting polypeptide or the BM -HABP polypeptide to identify a minimal domain for interaction. Alternatively, the two-hybrid  
15           system can be used to screen available organismal and/or mammalian tissue specific libraries of activation domain hybrids to identify polypeptides that bind to a BM -HABP polypeptide. These screens result in the immediate availability of the cloned gene for any new polypeptide identified. In addition, since multiple clones that encode overlapping regions of protein are  
20           often identified, the minimal domain for interaction may be readily apparent from the initial screen.

Assays may also be used that identify compounds which bind to full-length WF-HABP gene regulatory sequences (e.g., promoter or enhancer sequences) and which may modulate full-length WF-HABP gene expression. See e.g., Platt, J. Biol. Chem. 269:28558-28562  
25           (1994), which is incorporated herein by reference in its entirety.

Assays may also be used that identify compounds which bind to WF-HABP gene regulatory sequences (e.g., promoter or enhancer sequences) and which may modulate WF-HABP gene expression. See e.g., Platt, J. Biol. Chem. 269:28558-28562 (1994), which is incorporated herein by reference in its entirety.

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Assays may also be used that identify compounds which bind to BM-HABP gene regulatory sequences (e.g., promoter or enhancer sequences) and which may modulate BM-HABP gene expression. See e.g., Platt, J. Biol. Chem. **269**:28558-28562 (1994), which is incorporated herein by reference in its entirety.

5       The screening assays can be conducted in a variety of ways. For example, one method to conduct such an assay would involve anchoring the full-length WF-HABP polypeptide (e.g., fusion protein) or the test substance onto a solid phase and detecting full-length WF-HABP/test compound complexes anchored on the solid phase at the end of the reaction. In one embodiment of such a method, the full-length WF-HABP reactant may be anchored onto a  
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30       In practice, microtiter plates may conveniently be utilized as the solid phase. The anchored component may be immobilized by non-covalent or covalent attachments. Non-covalent attachment may be accomplished by simply coating the solid surface with a solution of the polypeptide and drying. Alternatively, an immobilized antibody, preferably a monoclonal

antibody, specific for the polypeptide to be immobilized may be used to anchor the polypeptide to the solid surface. The surfaces may be prepared in advance and stored.

In order to conduct the assay, the nonimmobilized component is added to the coated surface containing the anchored component. After the reaction is complete, unreacted components are removed (e.g., by washing) under conditions such that any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the previously nonimmobilized component is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the previously nonimmobilized component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; e.g., using a labeled antibody specific for the previously nonimmobilized component (the antibody, in turn, may be directly labeled or indirectly labeled with a labeled anti-Ig antibody).

Alternatively, a reaction can be conducted in a liquid phase, the reaction products separated from unreacted components, and complexes detected; e.g., using an immobilized antibody specific for full-length WF-HABP polypeptide or fusion protein or the test compound to anchor any complexes formed in solution, and a labeled antibody specific for the other component of the possible complex to detect anchored complexes.

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Alternatively, cell-based assays can be used to identify compounds that interact with WF-HABP. Such cell-based systems can include, for example, recombinant or non-recombinant cells, such as cell lines, which express the WF-HABP. For example spleen, lymph node, peripheral blood leukocytes, lung, thymus, heart, placenta, brain, bone marrow, and liver cells, or cell lines derived from spleen, lymph node, peripheral blood leukocytes, lung, thymus, heart, placenta, brain, bone marrow, and liver cells can be used. In addition, expression host cells (e.g., COS cells, CHO cells, HEK 293 cells, fibroblasts) genetically engineered (e.g., by transfection or transduction of WF-HABP DNA) to express a functional WF-HABP and to respond to activation by the natural WF-HABP ligand (e.g., a vanilloid compound, such as, for example, capsaicin), e.g., as measured by a chemical or phenotypic change, induction of another host cell gene, change in ion flux (e.g.,  $\text{Ca}^{+2}$ ), etc., can be used as an end point in the assay. Interaction of the test compound with, for example, one or more WF-HABP extracellular domains expressed by the host cell can be determined by comparison or competition with WF-HABP ligands (e.g., vanilloid compounds such as, capsaicin), by the ability to induce a WF-HABP mediated cellular response (e.g., ion (e.g.,  $\text{Ca}^{+2}$ ) flux), and other techniques known in the art. (See generally Caterina et al., Nature 389:816-824 (1997) which is herein incorporated by reference in its entirety). Thus, the present invention also provides a screening method for identifying compounds capable eliciting a cellular response induced by WF-HABP receptors, which involves contacting cells which express WF-HABP with the candidate compound, and comparing the cellular response to that observed in absence of the candidate compound (i.e., the standard); whereby, an increased cellular response over the standard indicates that the compound is an agonist.

Cellular responses that may be assayed according to this embodiment, include, but are not limited to alterations in the expression of the WF-HABP gene, e.g., by assaying cell lysates for WF-HABP mRNA transcripts (e.g., by Northern analysis) or for WF-HABP expressed in the cell; compounds which regulate or modulate expression of the WF-HABP gene are good candidates as therapeutics. Additionally, activity of the WF-HABP signal transduction pathway itself (e.g., cation flux, such as calcium flux) can be routinely assayed using techniques known in the art (see, e.g., Caterina et al., Nature 389:816-824 (1997), the contents of which are herein incorporated by reference in its entirety).

In another embodiment, the present invention is directed to a method for inhibiting an activity (e.g., ion flux (e.g.,  $\text{Ca}^{+2}$ ) flux), of WF-HABP induced by a WF-HABP ligand or WF-HABP stimulus (e.g., temperature), which involves administering to a cell which

expresses a WF-HABP polypeptide, an effective amount of a WF-HABP receptor ligand, analog or an antagonist capable of decreasing WF-HABP mediated signaling. Preferably, WF-HABP receptor mediated signaling is decreased to treat a disease wherein increased ion flux is exhibited. An antagonist can include soluble forms of the WF-HABP and antibodies directed  
 5 against the WF-HABP polypeptides which block WF-HABP receptor mediated signaling. Preferably, WF-HABP receptor mediated signaling is decreased to treat a disease, or to decrease survival, secretion, proliferation, migration and/or differentiation of cells.

In an additional embodiment, the present invention is directed to a method for increasing an activity (e.g., ion (e.g.,  $\text{Ca}^{+2}$ ) flux), induced by a WF-HABP ligand (e.g., a  
 10 vanilloid, such as, capsaicin) or WF-HABP stimulus (e.g., heat), which involves administering to a cell which expresses a WF-HABP polypeptide an effective amount of an agonist capable of increasing WF-HABP receptor mediated signaling. Preferably, WF-HABP receptor mediated signaling is increased to treat a disease wherein decreased ion flux is exhibited. Agonists of the present invention include monoclonal antibodies directed against the  
 15 WF-HABP polypeptides which stimulate WF-HABP receptor mediated signaling. Preferably, WF-HABP receptor mediated signaling is increased to treat a disease, and to increase survival, secretion, proliferation, migration, and/or differentiation of cells.

By "agonist" is intended naturally occurring and synthetic compounds capable of eliciting or enhancing ion (e.g.,  $\text{Ca}^{+2}$ ) flux mediated by WF-HABP polypeptides. Such  
 20 agonists include agents which increase expression of WF-HABP receptors or increase the sensitivity of the expressed receptor. By "antagonist" is intended naturally occurring and synthetic compounds capable of inhibiting WF-HABP mediated ion (e.g.,  $\text{Ca}^{+2}$ ) flux. Such antagonists include agents which decrease expression of WF-HABP receptors or decrease the sensitivity of the expressed receptor. Whether any candidate "agonist" or "antagonist" of the  
 25 present invention can enhance or inhibit a WF-HABP mediated cellular response, such as, for example, ion flux, and cell proliferation, survival, and differentiation can be determined using art-known ligand/receptor cellular response assays, and ion flux assays, including those described herein.

Thus, the present invention also provides a screening method for identifying  
 30 compounds capable of enhancing or inhibiting a cellular response induced by WF-HABP receptors. The method involves contacting cells which express WF-HABP polypeptides with the candidate compound in the presence of a WF-HABP ligand (e.g., a vanilloid compound, such as, capsaicin) or other stimulus (e.g., heat), assaying a cellular response (e.g., ion

(e.g.,  $\text{Ca}^{+2}$ ) flux), and comparing the cellular response to a standard cellular response, the standard being assayed when contact is made between the WF-HABP ligand and WF-HABP, or when WF-HABP is exposed to the stimulus, in absence of the candidate compound; whereby, an increased cellular response over the standard indicates that the compound is an agonist of the WF-HABP-mediated signaling pathway and a decreased cellular response over the standard indicates that the compound is an antagonist of the WF-HABP-mediated signaling pathway. By "assaying a cellular response" is intended qualitatively or quantitatively measuring a cellular response to a candidate compound and/or a WF-HABP ligand or WF-HABP stimulus (e.g., determining or estimating an increase or decrease in ion (e.g.,  $\text{Ca}^{+2}$ ) flux). By the invention, a cell expressing a WF-HABP polypeptide can be contacted with either an endogenous or exogenously administered WF-HABP ligand.

One such screening technique involves the use of cells which express the receptor (for example, transfected kidney-derived HEK293 cells) in a system which measures intracellular  $\text{Ca}^{+2}$  changes caused by receptor activation, for example, as described Caterina et al., Nature, 389:816-824 (1997). For example, compounds may be contacted with a cell which expresses the WF-HABP polypeptide of the present invention and ion (e.g.,  $\text{Ca}^{+2}$ ) flux, may be measured to determine whether the potential compound activates (i.e., leads to elevated ion flux) or inhibits the receptor.

Another method involves screening for compounds which inhibit activation of the receptor polypeptide of the present invention (i.e., antagonists) by determining inhibition of binding of labeled ligand to cells which have the receptor on the surface thereof. Such a method involves transfecting a eukaryotic cell with DNA encoding the WF-HABP polypeptide such that the cell expresses the receptor on its surface and contacting the cell with a compound in the presence of a labeled form of a WF-HABP ligand (e.g., a vanilloid compound, such as capsaicin). The ligand can be labeled, e.g., by radioactivity. The amount of labeled ligand bound to the receptors is measured, e.g., by measuring radioactivity of the WF-HABP polypeptide. If the compound binds to the receptor as determined by a reduction of labeled ligand which binds to the receptors, the binding of labeled ligand to the WF-HABP polypeptide is inhibited.

Soluble forms of the polypeptides of the present invention may be utilized in the ligand binding assay described above. These forms of WF-HABP are contacted with ligands in the extracellular medium after they are secreted. A determination is then made as to whether the secreted protein will bind to WF-HABP receptor ligands.

Agonists according to the present invention include compounds such as, for example, vanilloid receptor ligand peptide fragments, and neurotransmitters. Preferred agonists include WF-HABP polypeptide fragments of the invention and/or polyclonal and monoclonal antibodies raised against a WF-HABP polypeptide, or a fragment thereof.

5 WF-HABP polypeptides and polynucleotides and compounds identified as WF-HABP agonists or antagonists using assays described herein or otherwise known in the art, have uses which include, but are not limited to, treating diseases, regulating hematopoiesis, regulating immune responses, regulating cell survival, activation, secretion, migration and differentiation, regulating pain, and in developing analgesic agents and in furthering our  
10 understanding of pain insensitivity and pain syndromes.

### **Prophylactic and Therapeutic Methods**

It is to be understood that although the following discussion is specifically directed to human patients, the teachings are also applicable to any animal that expresses the full-length  
15 WF-HABP.

As noted above, the full-length WF-HABP is structurally related to members of the hyaluronan receptor family and shares significant homology with the human TSG-6 and link proteins which have been demonstrated to be involved in the formation and stability of the extracellular matrix, cellular migration, cellular proliferation, cellular adhesion, and is believed  
20 to be involved in diverse human diseases which include, but are not limited to arthritis, delayed-type hypersensitivity reactions, integumentary disorders, hematopoiesis, lymphocyte activation, inflammatory conditions, vascular disorders, and metastasis. Thus, it is likely that the full-length WF-HABP is active in modulating growth regulatory activities (e.g., cell survival, secretion, differentiation and/or cell proliferation). Further, the full-length WF-  
25 HABP, like TSG-6, might be involved in the adhesion and migration of cells which leads to conditions such as inflammation and ischemia. Correspondingly, the novel expression profile of full-length WF-HABP suggests that it may play a role in a broader variety of cell types than observed for TSG-6. Particularly, the full-length WF-HABP is expressed on vascular and non-vascular tissues and cells, though most notably in vascular tissues such as heart, placenta,  
30 lung, liver, kidney, human umbilical vein endothelial cells (HUVEC), and smooth muscle cells (SMC). Thus, the full-length WF-HABP plays a potential role in regulating a variety of cellular functions, particularly cellular adhesion for cells, such as, vascular cells (e.g., HUVEC, SMC, etc.), and this interaction is likely to result in activation, survival, proliferation, migration, and

differentiation, as well as the regulation of cytokine profiles by such cells. The full-length WF-HABP potentially mediates the interaction of other cells to cells in which the full-length WF-HABP is expressed. Thus the full-length WF-HABP is likely to play a role in influencing various diseases or medical conditions, including, but not limited to, inflammation, host defense, immune surveillance, arthritis, MS, autoimmunity, immune dysfunction, and allergy. Additionally, the full-length WF-HABP appears to be expressed in other cell populations (e.g., endothelial cells, mesenchymal cells, epithelial cells, muscular) and thus the full-length WF-HABP likely regulates adhesion onto these cells, thereby regulating their survival, differentiation, morphology, and proliferation. Accordingly, it is likely that the full-length WF-HABP plays a role in other physiological or disease conditions, including, cancer, angiogenesis, wound healing, fibrosis, metastasis and tissue regeneration.

As noted above, the WF-HABP is structurally related to members of the hyaluronan receptor family and shares significant homology with the human TSG-6 and link proteins which have been demonstrated to be involved in the formation and stability of the extracellular matrix, cellular migration, cellular proliferation, cellular adhesion, and is believed to be involved in diverse human diseases which include, but are not limited to arthritis, delayed-type hypersensitivity reactions, integumentary disorders, hematopoiesis, lymphocyte activation, inflammatory conditions, vascular disorders, and metastasis. Thus, it is likely that the WF-HABP is active in modulating growth regulatory activities (e.g., cell survival, secretion, differentiation and/or cell proliferation). Further, the WF-HABP, like TSG-6, might be involved in the adhesion and migration of cells which leads to conditions such as inflammation and ischemia. Correspondingly, the novel expression profile of WF-HABP suggests that it may play a role in a broader variety of cell types than observed for TSG-6. Particularly, the WF-HABP is expressed on vascular and non-vascular tissues and cells, though most notably in vascular tissues such as heart, placenta, lung, liver, kidney, human umbilical vein endothelial cells (HUVEC), and smooth muscle cells (SMC). Thus, the WF-HABP plays a potential role in regulating a variety of cellular functions, particularly cellular adhesion for cells, such as, vascular cells (e.g., HUVEC, SMC, etc.), and this interaction is likely to result in activation, survival, proliferation, migration, and differentiation, as well as the regulation of cytokine profiles by such cells. WF-HABP potentially mediates the interaction of other cells to cells in which WF-HABP is expressed. Thus the WF-HABP is likely to play a role in influencing various diseases or medical conditions, including, but not limited to, inflammation, host defense, immune surveillance, arthritis, MS, autoimmunity, immune dysfunction, and

allergy. Additionally, the WF-HABP appears to be expressed in other cell populations (e.g., endothelial cells, mesenchymal cells, epithelial cells, muscular) and thus the WF-HABP likely regulates adhesion onto these cells, thereby regulating their survival, differentiation, morphology, and proliferation. Accordingly, it is likely that the WF-HABP plays a role in other physiological or disease conditions, including, cancer, angiogenesis, wound healing, fibrosis, metastasis and tissue regeneration.

As noted above, the OE-HABP is structurally related to members of the hyaluronan receptor family and shares significant homology with the cartilage link proteins which have been demonstrated to be involved in the formation and stability of the extracellular matrix, cellular migration, cellular proliferation, cellular adhesion, and is believed to be involved in diverse human diseases which include, but are not limited to arthritis, delayed-type hypersensitivity reactions, integumentary disorders, hematopoiesis, lymphocyte activation, inflammatory conditions, vascular disorders, and metastasis. Thus, it is likely that the OE-HABP is active in modulating growth regulatory activities (e.g., cell survival, secretion, differentiation and/or cell proliferation). Further, the OE-HABP, like Link, might be involved in the adhesion and migration of cells which leads to conditions such as inflammation and ischemia. Correspondingly, the novel expression profile of OE-HABP suggests that it may play a role in a broader variety of cell types than observed for the link protein. Particularly, the OE-HABP is expressed on vascular and non-vascular tissues and cells, though most notably in vascular tissues such as heart, placenta, lung, human umbilical vein endothelial cells (HUVEC), and smooth muscle cells (SMC). Thus, the OE-HABP plays a potential role in regulating a variety of cellular functions, particularly cellular adhesion for cells, such as, vascular cells (e.g., HUVEC, SMC, etc.), and this interaction is likely to result in activation, survival, proliferation, migration, and differentiation, as well as the regulation of cytokine profiles by such cells. OE-HABP potentially mediates the interaction of other cells to cells in which OE-HABP is expressed. Thus the OE-HABP is likely to play a role in influencing various diseases or medical conditions, including, but not limited to, inflammation, host defense, immune surveillance, arthritis, MS, autoimmunity, immune dysfunction, and allergy. In fact, link protein is thought to be a potential autoantigen in the development of arthritis and ankylosing spondylitis, and therefore, OE-HABP may play a role in the pathogenesis of these diseases. Additionally, the OE-HABP appears to be expressed in other cell populations (e.g., endothelial cells, mesenchymal cells, epithelial cells, muscular) and thus the OE-HABP likely regulates adhesion onto these cells, thereby regulating their survival, differentiation,

morphology, and proliferation. Accordingly, it is likely that the OE-HABP plays a role in other physiological or disease conditions, including, cancer, angiogenesis, wound healing, fibrosis, metastasis and tissue regeneration.

As noted above, the BM-HABP is structurally related to members of the hyaluronan receptor family and shares significant homology with the TSG-6 proteins which have been demonstrated to be involved in the formation and stability of the extracellular matrix, cellular migration, cellular proliferation, cellular adhesion, and is believed to be involved in diverse human diseases which include, but are not limited to arthritis, delayed-type hypersensitivity reactions, integumentary disorders, hematopoiesis, lymphocyte activation, inflammatory conditions, vascular disorders, and metastasis. Thus, it is likely that the BM-HABP is active in modulating growth regulatory activities (e.g., cell survival, secretion, differentiation and/or cell proliferation). Further, the BM-HABP, like TSG-6, might be involved in the adhesion and migration of cells which leads to conditions such as inflammation and ischemia. Correspondingly, the novel expression profile of BM-HABP suggests that it may play a role in a broader variety of cell types than observed for TSG-6. Particularly, the BM-HABP is expressed in liver tissue. Unlike TSG-6, significant expression within vascular tissues was not detected suggesting BM-HABP may play a more divergent role in other tissues. However, based upon the structural similarity to TSG-6, BM-HABP may play a potential role in regulating a variety of cellular functions, particularly cellular adhesion for cells, such as, endothelial cells (e.g., liver, etc.), and this interaction is likely to result in activation, survival, proliferation, migration, and differentiation, as well as the regulation of cytokine profiles by such cells. Thus the BM-HABP is likely to play a role in influencing various diseases or medical conditions, including, but not limited to, inflammation, host defense, immune surveillance, arthritis, MS, autoimmunity, immune dysfunction, and allergy. Additionally, the BM-HABP appears to be expressed in other cell populations (e.g., endothelial cells, mesenchymal cells, epithelial cells, metabolic) and thus the BM-HABP likely regulates adhesion onto these cells, thereby regulating their survival, differentiation, morphology, and proliferation. Accordingly, it is likely that the BM-HABP plays a role in other physiological or disease conditions, including, cancer, angiogenesis, wound healing, fibrosis, metastasis and tissue regeneration.

Any method which neutralizes or enhances full-length WF-HABP mediated signaling can be used to modulate growth regulatory activities (e.g., cell proliferation, metastasis), and other activities mediated by full-length WF-HABP activity, such as, for example,

extravasation, inflammation, host defense, immune surveillance, arthritis, MS, autoimmunity, immune dysfunction, allergy, cancer, angiogenesis, wound healing, water homeostasis, macromolecular filtration, lubrication, fibrosis, and tissue regeneration.

Any method which neutralizes or enhances WF-HABP mediated signaling can be used to modulate growth regulatory activities (e.g., cell proliferation, metastasis), and other activities mediated by WF-HABP activity, such as, for example, extravasation, inflammation, host defense, immune surveillance, arthritis, MS, autoimmunity, immune dysfunction, allergy, cancer, angiogenesis, wound healing, water homeostasis, macromolecular filtration, lubrication, fibrosis, and tissue regeneration.

Any method which neutralizes or enhances OE-HABP mediated signaling can be used to modulate growth regulatory activities (e.g., cell proliferation, metastasis), and other activities mediated by OE-HABP activity, such as, for example, extravasation, inflammation, host defense, immune surveillance, arthritis, MS, autoimmunity, immune dysfunction, allergy, cancer, angiogenesis, wound healing, water homeostasis, macromolecular filtration, lubrication, fibrosis, and tissue regeneration.

Any method which neutralizes or enhances BM-HABP mediated signaling can be used to modulate growth regulatory activities (e.g., cell proliferation, metastasis), and other activities mediated by BM-HABP activity, such as, for example, extravasation, inflammation, host defense, immune surveillance, arthritis, MS, autoimmunity, immune dysfunction, allergy, cancer, angiogenesis, wound healing, water homeostasis, macromolecular filtration, lubrication, fibrosis, and tissue regeneration.

Full-length WF-HABP polynucleotides or polypeptides (including full-length WF-HABP fragments, variants, derivatives, and analogs, and full-length WF-HABP agonists and antagonists as described herein) may be useful in treating disorders associated with rheological aberrations, autoimmunity, inflammation, proliferation and metastasis. Additionally, these compounds may be useful in treating, preventing, or activating cell death (e.g., of hematopoietic cells during processes of inflammation or tissue injury).

WF-HABP polynucleotides or polypeptides (including WF-HABP fragments, variants, derivatives, and analogs, and WF-HABP agonists and antagonists as described herein) may be useful in treating disorders associated with rheological aberrations, autoimmunity, inflammation, proliferation and metastasis. Additionally, these compounds may be useful in treating, preventing, or activating cell death (e.g., of hematopoietic cells during processes of inflammation or tissue injury).



OE-HABP polynucleotides or polypeptides (including OE-HABP fragments, variants, derivatives, and analogs, and OE-HABP agonists and antagonists as described herein) may be useful in treating disorders associated with rheological aberrations, autoimmunity, inflammation, proliferation and metastasis. Additionally, these compounds may be useful in

5 treating, preventing, or activating cell death (e.g., of hematopoietic cells during processes of inflammation or tissue injury).

BM-HABP polynucleotides or polypeptides (including BM-HABP fragments, variants, derivatives, and analogs, and BM-HABP agonists and antagonists as described herein) may be useful in treating disorders associated with rheological aberrations, autoimmunity,

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Full-length WF-HABP polynucleotides or polypeptides (including full-length WF-HABP fragments, variants, derivatives, and analogs, and full-length WF-HABP agonists and

15 antagonists as described herein) may be useful in treating disorders associated with extracellular matrix genesis, integumentary disorders, edema, hemophilia, and hydrovasation. Additionally, these compounds may be useful in treating, preventing, or activating cell migration (e.g., of hematopoietic cells during processes of inflammation or tissue injury). Such traits would particularly be useful when cells, near sites of surgery or injury, are induced

20 to express full-length WF-HABP polynucleotides or polypeptides. Due to the exclusionary, and water homeostasis properties of members of the HA receptor family, such expression could inhibit vascular leakage of interstitial, plasma, blood, or other bodily fluid, while simultaneously recruiting immune and/or hematopoietic cells.

WF-HABP polynucleotides or polypeptides (including WF-HABP fragments, variants,

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BM-HABP polynucleotides or polypeptides (including BM-HABP fragments, variants, derivatives, and analogs, and BM-HABP agonists and antagonists as described herein) may be useful in treating disorders associated with extracellular matrix genesis, integumentary disorders, edema, hemophilia, and hydrovasation. Additionally, these compounds may be useful in treating, preventing, or activating cell migration (e.g., of hematopoietic cells during processes of inflammation or tissue injury). Such traits would particularly be useful when cells, near sites of surgery or injury, are induced to express BM-HABP polunucleotides or polypeptides. Due to the exclusionary, and water homeostasis properties of members of the HA receptor family, such expression could inhibit vascular leakage of interstitial, plasma, blood, or other bodily fluid, while simulatanously recruiting immune and/or hematopoietic cells.

Similarly, full-length WF-HABP polynucleotides or polypeptides (including full-length WF-HABP fragments, variants, derivatives, and analogs, and full-length WF-HABP agonists and antagonists as described herein) may be useful in treating disorders associated with hemophilial conditions, since HA receptor members have been shown to maintain separation of integumentary surfaces during shear, blunt, and viscous forces which may inhibit the likelihood of injury by establishing a lubricative benefit to the immediate tissues.

Similarly, WF-HABP polynucleotides or polypeptides (including WF-HABP fragments, variants, derivatives, and analogs, and WF-HABP agonists and antagonists as described herein) may be useful in treating disorders associated with hemophilial conditions,

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Similarly, BM-HABP polynucleotides or polypeptides (including BM-HABP fragments, variants, derivatives, and analogs, and BM-HABP agonists and antagonists as described herein) may be useful in treating disorders associated with hemophilial conditions, since HA receptor members have been shown to maintain separation of integumentary surfaces during shear, blunt, and viscous forces which may inhibit the likelihood of injury by establishing a lubricative benefit to the immediate tissues.

Full-length WF-HABP polypeptides or polynucleotides (including full-length WF-HABP fragments, variants, derivatives, and analogs, and full-length WF-HABP agonists and antagonists as described herein) may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, full-length WF-HABP polynucleotides or polypeptides can be used as a marker or detector of a particular immune system disease or disorder.

WF-HABP polypeptides or polynucleotides (including WF-HABP fragments, variants, derivatives, and analogs, and WF-HABP agonists and antagonists as described herein) may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic,

such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, WF-HABP polynucleotides or polypeptides can be used as a marker or detector of a particular immune system disease or disorder.

OE-HABP polypeptides or polynucleotides (including OE-HABP fragments, variants, derivatives, and analogs, and OE-HABP agonists and antagonists as described herein) may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, OE-HABP polynucleotides or polypeptides can be used as a marker or detector of a particular immune system disease or disorder.

BM-HABP polypeptides or polynucleotides (including BM-HABP fragments, variants, derivatives, and analogs, and BM-HABP agonists and antagonists as described herein) may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, BM-HABP polynucleotides or polypeptides can be used as a marker or detector of a particular immune system disease or disorder.

Full-length WF-HABP polypeptides or polynucleotides (including full-length WF-HABP fragments, variants, derivatives, and analogs, and full-length WF-HABP agonists and antagonists as described herein) may be useful in treating deficiencies or disorders of the integumentary system, by activating or inhibiting the proliferation, differentiation, or growth of integumentary cells and tissues, in addition to stimulating the development of the extracellular matrix. Hyaluronan, and thus HA receptors, are known to play an integral role in the development of the extracellular matrix which provides, for example, exclusionary benefits to the surrounding cells and tissues. Thus, such a barrier serves to protect cells behind its protective cloak from immune cell damage or detection, impedes viral infection through exclusion of the infectious particles, and may provide enabling benefit to cells during growth

cycles, such as during mitosis. The etiology of these integumentary deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins or radiation), or infectious. Moreover, full-length WF-HABP polynucleotides or polypeptides can be used as a marker or detector of a particular integumentary system disease or disorder.

WF-HABP polypeptides or polynucleotides (including WF-HABP fragments, variants, derivatives, and analogs, and WF-HABP agonists and antagonists as described herein) may be useful in treating deficiencies or disorders of the integumentary system, by activating or inhibiting the proliferation, differentiation, or growth of integumentary cells and tissues, in addition to stimulating the development of the extracellular matrix. Hyaluronan, and thus HA receptors, are known to play an integral role in the development of the extracellular matrix which provides, for example, exclusionary benefits to the surrounding cells and tissues. Thus, such a barrier serves to protect cells behind its protective cloak from immune cell damage or detection, impedes viral infection through exclusion of the infectious particles, and may provide enabling benefit to cells during growth cycles, such as during mitosis. The etiology of these integumentary deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins or radiation), or infectious. Moreover, WF-HABP polynucleotides or polypeptides can be used as a marker or detector of a particular integumentary system disease or disorder.

OE-HABP polypeptides or polynucleotides (including OE-HABP fragments, variants, derivatives, and analogs, and OE-HABP agonists and antagonists as described herein) may be useful in treating deficiencies or disorders of the integumentary system, by activating or inhibiting the proliferation, differentiation, or growth of integumentary cells and tissues, in addition to stimulating the development of the extracellular matrix. Hyaluronan, and thus HA receptors, are known to play an integral role in the development of the extracellular matrix which provides, for example, exclusionary benefits to the surrounding cells and tissues. Thus, such a barrier serves to protect cells behind its protective cloak from immune cell damage or detection, impedes viral infection through exclusion of the infectious particles, and may provide enabling benefit to cells during growth cycles, such as during mitosis. The etiology of these integumentary deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins or radiation), or infectious. Moreover, OE-HABP polynucleotides or polypeptides can be used as a marker or detector of a particular integumentary system disease or disorder.

BM-HABP polypeptides or polynucleotides (including BM-HABP fragments, variants, derivatives, and analogs, and BM-HABP agonists and antagonists as described herein) may be useful in treating deficiencies or disorders of the integumentary system, by activating or inhibiting the proliferation, differentiation, or growth of integumentary cells and tissues, in addition to stimulating the development of the extracellular matrix. Hyaluronan, and thus HA receptors, are known to play an integral role in the development of the extracellular matrix which provides, for example, exclusionary benefits to the surrounding cells and tissues. Thus, such a barrier serves to protect cells behind its protective cloak from immune cell damage or detection, impedes viral infection through exclusion of the infectious particles, and may provide enabling benefit to cells during growth cycles, such as during mitosis. The etiology of these integumentary deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins or radiation), or infectious. Moreover, BM-HABP polynucleotides or polypeptides can be used as a marker or detector of a particular integumentary system disease or disorder.

Full-length WF-HABP polynucleotides or polypeptides (including full-length WF-HABP fragments, variants, derivatives, and analogs, and full-length WF-HABP agonists and antagonists as described herein) may be useful in treating or detecting deficiencies or disorders of hematopoietic cells. As further discussed below, full-length WF-HABP polypeptides, polynucleotides, and/or full-length WF-HABP agonists or antagonists could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types of hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria. Moreover, full-length WF-HABP polypeptides, polynucleotides and/or full-length WF-HABP antagonists can be used to infections of viral, bacterial, or fungal origins through exclusion. Additionally, full-length WF-HABP polypeptides, polynucleotides and/or full-length WF-HABP antagonists can be used to treat or prevent the killing of hematopoietic cells and other cells during processes of inflammation or tissue injury.

WF-HABP polynucleotides or polypeptides (including WF-HABP fragments, variants, derivatives, and analogs, and WF-HABP agonists and antagonists as described herein) may be useful in treating or detecting deficiencies or disorders of hematopoietic cells. As further discussed below, WF-HABP polypeptides, polynucleotides, and/or WF-HABP agonists or antagonists could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types of hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria. Moreover, WF-HABP polypeptides, polynucleotides and/or WF-HABP antagonists can be used to infections of viral, bacterial, or fungal origins through exclusion. Additionally, WF-HABP polypeptides, polynucleotides and/or WF-HABP antagonists can be used to treat or prevent the killing of hematopoietic cells and other cells during processes of inflammation or tissue injury.

OE-HABP polynucleotides or polypeptides (including OE-HABP fragments, variants, derivatives, and analogs, and OE-HABP agonists and antagonists as described herein) may be useful in treating or detecting deficiencies or disorders of hematopoietic cells. As further discussed below, OE-HABP polypeptides, polynucleotides, and/or OE-HABP agonists or antagonists could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types of hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria. Moreover, OE-HABP HABP polypeptides, polynucleotides and/or OE-HABP antagonists can be used to infections of viral, bacterial, or fungal origins through exclusion. Additionally, OE-HABP polypeptides, polynucleotides and/or OE-HABP

antagonists can be used to treat or prevent the killing of hematopoietic cells and other cells during processes of inflammation or tissue injury.

BM-HABP polynucleotides or polypeptides (including BM-HABP fragments, variants, derivatives, and analogs, and BM-HABP agonists and antagonists as described herein) may be useful in treating or detecting deficiencies or disorders of hematopoietic cells. As further discussed below, BM-HABP polypeptides, polynucleotides, and/or BM-HABP agonists or antagonists could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types of hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria. Moreover, BM-HABP HABP polypeptides, polynucleotides and/or BM-HABP antagonists can be used to infections of viral, bacterial, or fungal origins through exclusion. Additionally, BM-HABP polypeptides, polynucleotides and/or BM-HABP antagonists can be used to treat or prevent the killing of hematopoietic cells and other cells during processes of inflammation or tissue injury.

Moreover, full-length WF-HABP polypeptides or polynucleotides (including full-length WF-HABP fragments, variants, derivatives, and analogs, and full-length WF-HABP agonists and antagonists as described herein) can also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, full-length WF-HABP polynucleotides or polypeptides could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, full-length WF-HABP polynucleotides, polypeptides and/or full-length WF-HABP agonists or antagonists that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting, important in the treatment of heart attacks (infarction), strokes, or scarring.

Moreover, WF-HABP polypeptides or polynucleotides (including WF-HABP fragments, variants, derivatives, and analogs, and WF-HABP agonists and antagonists as described herein) can also be used to modulate hemostatic (the stopping of bleeding) or



thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, WF-HABP polynucleotides or polypeptides could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, 5 WF-HABP polynucleotides, polypeptides and/or WF-HABP agonists or antagonists that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting, important in the treatment of heart attacks (infarction), strokes, or scarring.

Moreover, OE-HABP polypeptides or polynucleotides (including OE-HABP fragments, variants, derivatives, and analogs, and OE-HABP agonists and antagonists as 10 described herein) can also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, OE-HABP polynucleotides or polypeptides could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, 15 OE-HABP polynucleotides, polypeptides and/or OE-HABP agonists or antagonists that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting, important in the treatment of heart attacks (infarction), strokes, or scarring.

Moreover, BM-HABP polypeptides or polynucleotides (including BM-HABP fragments, variants, derivatives, and analogs, and BM-HABP agonists and antagonists as 20 described herein) can also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, BM-HABP polynucleotides or polypeptides could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, 25 BM-HABP polynucleotides, polypeptides and/or BM-HABP agonists or antagonists that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting, important in the treatment of heart attacks (infarction), strokes, or scarring.

Full-length WF-HABP polynucleotides or polypeptides (including full-length WF-HABP fragments, variants, derivatives, and analogs, and full-length WF-HABP agonists or 30 full-length WF-HABP antagonists as described herein) may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the

administration of full-length WF-HABP polypeptides or polynucleotides and/or full-length WF-HABP agonists or full-length WF-HABP antagonists that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders. Examples of autoimmune disorders that can be

5 treated or detected by full-length WF-HABP include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome,

10 Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

WF-HABP polynucleotides or polypeptides (including WF-HABP fragments, variants, derivatives, and analogs, and WF-HABP agonists or WF-HABP antagonists as described

15 herein) may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of WF-HABP polypeptides or polynucleotides and/or WF-HABP agonists or WF-HABP antagonists that can inhibit an immune response,

20 particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders. Examples of autoimmune disorders that can be treated or detected by WF-HABP include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple

25 Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

30 OE-HABP polynucleotides or polypeptides (including OE-HABP fragments, variants, derivatives, and analogs, and OE-HABP agonists or OE-HABP antagonists as described herein) may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells.

This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of OE-HABP polypeptides or polynucleotides and/or OE-HABP agonists or OE-HABP antagonists that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders. Examples of autoimmune disorders that can be treated or detected by OE-HABP include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

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Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems may also be treated by full-length WF-HABP polypeptides, full-length WF-HABP polynucleotides or full-length WF-HABP agonists or full-

length WF-HABP antagonists. Moreover, full-length WF-HABP can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems may also be treated by WF-HABP polypeptides, WF-HABP polynucleotides or WF-HABP agonists or WF-HABP antagonists. Moreover, WF-HABP can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

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Full-length WF-HABP polynucleotides or polypeptides (including full-length WF-HABP fragments, variants, derivatives, and analogs, and full-length WF-HABP agonists and full-length WF-HABP antagonists as described herein) may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of full-length WF-HABP polypeptides or polynucleotides and/or full-length WF-HABP agonists or antagonists that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, including the ability of immune cells to bind to other cells, or the extracellular matrix, may be an effective therapy in preventing organ rejection or GVHD.

WF-HABP polynucleotides or polypeptides (including WF-HABP fragments, variants, derivatives, and analogs, and WF-HABP agonists and WF-HABP antagonists as described herein) may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but,

in this case, the foreign transplanted immune cells destroy the host tissues. The administration of WF-HABP polypeptides or polynucleotides and/or WF-HABP agonists or antagonists that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, including the ability of immune cells to bind to other cells, or the extracellular matrix, may be an effective therapy in preventing organ rejection or GVHD.

OE-HABP polynucleotides or polypeptides (including OE-HABP fragments, variants, derivatives, and analogs, and OE-HABP agonists and OE-HABP antagonists as described herein) may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of OE-HABP polypeptides or polynucleotides and/or OE-HABP agonists or antagonists that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, including the ability of immune cells to bind to other cells, or the extracellular matrix, may be an effective therapy in preventing organ rejection or GVHD.

BM-HABP polynucleotides or polypeptides (including BM-HABP fragments, variants, derivatives, and analogs, and BM-HABP agonists and BM-HABP antagonists as described herein) may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of BM-HABP polypeptides or polynucleotides and/or BM-HABP agonists or antagonists that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, including the ability of immune cells to bind to other cells, or the extracellular matrix, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, full-length WF-HABP polypeptides or polynucleotides (including full-length WF-HABP fragments, variants, derivatives, and analogs, and full-length WF-HABP agonists and full-length WF-HABP antagonists as described herein) may also be used to modulate inflammation. For example, full-length WF-HABP polypeptides or polynucleotides and/or full-length WF-HABP agonists and antagonists of the invention may inhibit the proliferation and differentiation of cells involved in an inflammatory response or alternatively may be involved in killing of hematopoietic cells during processes of inflammation or tissue injury. Moreover, full-length WF-HABP polypeptides or polynucleotides and/or full-length WF-

HABP agonists and antagonists of the invention may inhibit inflammation via steric exclusion of immune cells to sites of injury, inhibiting interaction of immune cells with the extracellular matrix, or by inhibiting immune cell locomotion and migration. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1). Additionally, these molecules may be used to treat or prevent killing of hematopoietic cells and/or other cells during processes of inflammation or tissue injury.

Similarly, WF-HABP polypeptides or polynucleotides (including WF-HABP fragments, variants, derivatives, and analogs, and WF-HABP agonists and WF-HABP antagonists as described herein) may also be used to modulate inflammation. For example, WF-HABP polypeptides or polynucleotides and/or WF-HABP agonists and antagonists of the invention may inhibit the proliferation and differentiation of cells involved in an inflammatory response or alternatively may be involved in killing of hematopoietic cells during processes of inflammation or tissue injury. Moreover, WF-HABP polypeptides or polynucleotides and/or WF-HABP agonists and antagonists of the invention may inhibit inflammation via steric exclusion of immune cells to sites of injury, inhibiting interaction of immune cells with the extracellular matrix, or by inhibiting immune cell locomotion and migration. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1). Additionally, these molecules may be used to treat or prevent killing of hematopoietic cells and/or other cells during processes of inflammation or tissue injury.

Similarly, OE-HABP polypeptides or polynucleotides (including OE-HABP fragments, variants, derivatives, and analogs, and OE-HABP agonists and OE-HABP antagonists as described herein) may also be used to modulate inflammation. For example, OE-HABP polypeptides or polynucleotides and/or OE-HABP agonists and antagonists of the invention may inhibit the proliferation and differentiation of cells involved in an inflammatory response

or alternatively may be involved in killing of hematopoietic cells during processes of inflammation or tissue injury. Moreover, OE-HABP polypeptides or polynucleotides and/or OE-HABP agonists and antagonists of the invention may inhibit inflammation via steric exclusion of immune cells to sites of injury, inhibiting interaction of immune cells with the extracellular matrix, or by inhibiting immune cell locomotion and migration. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1). Additionally, these molecules may be used to treat or prevent killing of hematopoietic cells and/or other cells during processes of inflammation or tissue injury.

Similarly, BM-HABP polypeptides or polynucleotides (including BM-HABP fragments, variants, derivatives, and analogs, and BM-HABP agonists and BM-HABP antagonists as described herein) may also be used to modulate inflammation. For example, BM-HABP polypeptides or polynucleotides and/or BM-HABP agonists and antagonists of the invention may inhibit the proliferation and differentiation of cells involved in an inflammatory response or alternatively may be involved in killing of hematopoietic cells during processes of inflammation or tissue injury. Moreover, BM-HABP polypeptides or polynucleotides and/or BM-HABP agonists and antagonists of the invention may inhibit inflammation via steric exclusion of immune cells to sites of injury, inhibiting interaction of immune cells with the extracellular matrix, or by inhibiting immune cell locomotion and migration. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1). Additionally, these molecules may be used to treat or prevent killing of hematopoietic cells and/or other cells during processes of inflammation or tissue injury.

Full-length WF-HABP polypeptides or polynucleotides (including full-length WF-HABP fragments, variants, derivatives, and analogs, and full-length WF-HABP agonists and

antagonists as described herein) can be used to treat or detect hyperproliferative disorders, including neoplasms. Full-length WF-HABP polypeptides or polynucleotides and/or full-length WF-HABP agonists or antagonists, may inhibit the proliferation of the disorder through direct or indirect interactions (e.g. inhibiting ability of proliferative cells to adhere to the tissue matrix or other cells). Alternatively, full-length WF-HABP polypeptides or polynucleotides and/or full-length WF-HABP agonists or antagonists may proliferate other cells which can inhibit the hyperproliferative disorder. For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

WF-HABP polypeptides or polynucleotides (including WF-HABP fragments, variants, derivatives, and analogs, and WF-HABP agonists and antagonists as described herein) can be used to treat or detect hyperproliferative disorders, including neoplasms. WF-HABP polypeptides or polynucleotides and/or WF-HABP agonists or antagonists, may inhibit the proliferation of the disorder through direct or indirect interactions (e.g. inhibiting ability of proliferative cells to adhere to the tissue matrix or other cells). Alternatively, WF-HABP polypeptides or polynucleotides and/or WF-HABP agonists or antagonists may proliferate other cells which can inhibit the hyperproliferative disorder. For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

OE-HABP polypeptides or polynucleotides (including OE-HABP fragments, variants, derivatives, and analogs, and OE-HABP agonists and antagonists as described herein) can be used to treat or detect hyperproliferative disorders, including neoplasms. OE-HABP polypeptides or polynucleotides and/or OE-HABP agonists or antagonists, may inhibit the proliferation of the disorder through direct or indirect interactions (e.g. inhibiting ability of proliferative cells to adhere to the tissue matrix or other cells). Alternatively, OE-HABP polypeptides or polynucleotides and/or OE-HABP agonists or antagonists may proliferate other



cells which can inhibit the hyperproliferative disorder. For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or  
5 by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

BM-HABP polypeptides or polynucleotides (including BM-HABP fragments, variants, derivatives, and analogs, and BM-HABP agonists and antagonists as described herein) can be used to treat or detect hyperproliferative disorders, including neoplasms. BM-HABP  
10 polypeptides or polynucleotides and/or BM-HABP agonists or antagonists, may inhibit the proliferation of the disorder through direct or indirect interactions (e.g. inhibiting ability of proliferative cells to adhere to the tissue matrix or other cells). Alternatively, BM-HABP polypeptides or polynucleotides and/or BM-HABP agonists or antagonists may proliferate other cells which can inhibit the hyperproliferative disorder. For example, by increasing an  
15 immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a  
20 chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by full-length WF-HABP polynucleotides or polypeptides and/or full-length WF-HABP agonists or antagonists include, but are not limited to, neoplasms located in the: blood, abdomen, bone, lung, breast, digestive system, liver, pancreas, prostate, peritoneum, endocrine glands  
25 (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, hematopoietic tissue, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Examples of hyperproliferative disorders that can be treated or detected by WF-HABP polynucleotides or polypeptides and/or WF-HABP agonists or antagonists include, but are not  
30 limited to, neoplasms located in the: blood, abdomen, bone, lung, breast, digestive system, liver, pancreas, prostate, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral),

lymphatic system, hematopoietic tissue, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Examples of hyperproliferative disorders that can be treated or detected by OE-HABP polynucleotides or polypeptides and/or OE-HABP agonists or antagonists include, but are not limited to, neoplasms located in the: blood, abdomen, bone, lung, breast, digestive system, liver, pancreas, prostate, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, hematopoietic tissue, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Examples of hyperproliferative disorders that can be treated or detected by BM-HABP polynucleotides or polypeptides and/or BM-HABP agonists or antagonists include, but are not limited to, neoplasms located in the: blood, abdomen, bone, lung, breast, digestive system, liver, pancreas, prostate, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, hematopoietic tissue, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by full-length WF-HABP polynucleotides or polypeptides and/or full-length WF-HABP agonists or antagonists. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

Similarly, other hyperproliferative disorders can also be treated or detected by WF-HABP polynucleotides or polypeptides and/or WF-HABP agonists or antagonists. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

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Waldenström's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

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Full-length WF-HABP polypeptides or polynucleotides (including full-length WF-HABP fragments, variants, derivatives, and analogs, and full-length WF-HABP agonists and antagonists as described herein) can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, full-length WF-HABP polypeptides or polynucleotides and/or full-length WF-HABP agonists or antagonists may also directly inhibit the infectious agent, without necessarily eliciting an immune response (e.g. enhancing the integrity of the extracellular matrix to efficiently occlude infectious agents).

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OE-HABP polypeptides or polynucleotides (including OE-HABP fragments, variants, derivatives, and analogs, and OE-HABP agonists and antagonists as described herein) can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, OE-HABP

polypeptides or polynucleotides and/or OE-HABP agonists or antagonists may also directly inhibit the infectious agent, without necessarily eliciting an immune response (e.g. enhancing the integrity of the extracellular matrix to efficiently occlude infectious agents).

BM-HABP polypeptides or polynucleotides (including BM-HABP fragments, variants, derivatives, and analogs, and BM-HABP agonists and antagonists as described herein) can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, BM-HABP polypeptides or polynucleotides and/or BM-HABP agonists or antagonists may also directly inhibit the infectious agent, without necessarily eliciting an immune response (e.g. enhancing the integrity of the extracellular matrix to efficiently occlude infectious agents).

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated by full-length WF-HABP polynucleotides or polypeptides and/or full-length WF-HABP agonists or antagonists. Examples of viruses, include, but are not limited to, the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. Full-length WF-HABP polypeptides or polynucleotides and/or full-length WF-HABP agonists or antagonists can be used to treat any of these symptoms or diseases.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated by WF-HABP polynucleotides or polypeptides and/or WF-HABP agonists or antagonists. Examples of viruses, include, but are not limited to, the following DNA and RNA

viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza),

5 Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic

10 Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. WF-HABP polypeptides or polynucleotides and/or WF-HABP agonists or antagonists can be used to treat any of these symptoms or diseases.

15 Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated by OE-HABP polynucleotides or polypeptides and/or OE-HABP agonists or antagonists. Examples of viruses, include, but are not limited to, the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis),

20 Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or

25 symptoms, including, but not limited to: arthritis, bronchiolitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g.,

30 Kaposi's, warts), and viremia. OE-HABP polypeptides or polynucleotides and/or OE-HABP agonists or antagonists can be used to treat any of these symptoms or diseases.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated by BM-HABP polynucleotides or polypeptides and/or BM-HABP agonists or

antagonists. Examples of viruses, include, but are not limited to, the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. BM-HABP polypeptides or polynucleotides and/or BM-HABP agonists or antagonists can be used to treat any of these symptoms or diseases.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated by full-length WF-HABP polynucleotides or polypeptides and/or full-length WF-HABP agonists or antagonists include, but are not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Pasteurellaceae Infections (e.g., Actinobacillus, Haemophilus, Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo,

Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. Full-length WF-HABP polypeptides or polynucleotides and/or full-length WF-HABP agonists or antagonists can be used to treat or detect any of these symptoms or diseases.

- 5 Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated by WF-HABP polynucleotides or polypeptides and/or WF-HABP agonists or antagonists include, but are not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., *Corynebacterium*, *Mycobacterium*, *Nocardia*), Aspergillosis, Bacillaceae (e.g., Anthrax, *Clostridium*), Bacteroidaceae, Blastomycosis, *Bordetella*, *Borrelia*, Brucellosis, Candidiasis, *Campylobacter*, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (*Klebsiella*, *Salmonella*, *Serratia*, *Yersinia*), *Erysipelothrix*, *Helicobacter*, Legionellosis, Leptospirosis, *Listeria*, Mycoplasmatales, Neisseriaceae (e.g., *Acinetobacter*, Gonorrhea, Meningococcal), Pasteurellaceae Infections (e.g., *Actinobacillus*, *Haemophilus*, *Pasteurella*), *Pseudomonas*, Rickettsiaceae, Chlamydiaceae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. WF-HABP polypeptides or polynucleotides and/or WF-HABP agonists or antagonists can be used to treat or detect any of these symptoms or diseases.

- 30 Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated by OE-HABP polynucleotides or polypeptides and/or OE-HABP agonists or antagonists include, but are not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., *Corynebacterium*, *Mycobacterium*, *Nocardia*), Aspergillosis, Bacillaceae (e.g., Anthrax, *Clostridium*), Bacteroidaceae, Blastomycosis, *Bordetella*, *Borrelia*, Brucellosis, Candidiasis, *Campylobacter*, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (*Klebsiella*,

Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Pasteurellaceae Infections (e.g., Actinobacillus, Haemophilus, Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. OE-HABP polypeptides or polynucleotides and/or OE-HABP agonists or antagonists can be used to treat or detect any of these symptoms or diseases.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated by BM-HABP polynucleotides or polypeptides and/or BM-HABP agonists or antagonists include, but are not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Pasteurellaceae Infections (e.g., Actinobacillus, Haemophilus, Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo,



Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. BM-HABP polypeptides or polynucleotides and/or BM-HABP agonists or antagonists can be used to treat or detect any of these symptoms or diseases.

5           Moreover, parasitic agents causing disease or symptoms that can be treated by full-length WF-HABP polynucleotides or polypeptides and/or WF-HABP agonists or antagonists include, but are not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas. These  
10 parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. full-length WF-HABP polypeptides or polynucleotides and/or full-length WF-HABP agonists or antagonists can be used to treat or detect any of these symptoms or  
15 diseases.

          Moreover, parasitic agents causing disease or symptoms that can be treated by WF-HABP polynucleotides or polypeptides and/or WF-HABP agonists or antagonists include, but are not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis,  
20 Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas. These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. WF-HABP polypeptides or polynucleotides and/or WF-HABP agonists or  
25 antagonists can be used to treat or detect any of these symptoms or diseases.

          Moreover, parasitic agents causing disease or symptoms that can be treated by OE-HABP polynucleotides or polypeptides and/or OE-HABP agonists or antagonists include, but are not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis,  
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and toxoplasmosis. OE-HABP polypeptides or polynucleotides and/or OE-HABP agonists or antagonists can be used to treat or detect any of these symptoms or diseases.

Moreover, parasitic agents causing disease or symptoms that can be treated by BM-HABP polynucleotides or polypeptides and/or BM-HABP agonists or antagonists include, but are not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas. These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. BM-HABP polypeptides or polynucleotides and/or BM-HABP agonists or antagonists can be used to treat or detect any of these symptoms or diseases.

Full-length WF-HABP polynucleotides or polypeptides (including full-length WF-HABP fragments, variants, derivatives, and analogs, and full-length WF-HABP agonists and antagonists as described herein) can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997). The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage. Tissues that may be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vascular (including vascular endothelium), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis. Additionally, these compounds can be used to treat or prevent cell death (e.g., hematopoietic cell death) during processes of inflammation or tissue injury.

WF-HABP polynucleotides or polypeptides (including WF-HABP fragments, variants, derivatives, and analogs, and WF-HABP agonists and antagonists as described herein) can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997). The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that may be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vascular (including vascular endothelium), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring.

- 5   Regeneration also may include angiogenesis. Additionally, these compounds can be used to treat or prevent cell death (e.g., hematopoietic cell death) during processes of inflammation or tissue injury.

OE-HABP polynucleotides or polypeptides (including OE-HABP fragments, variants, derivatives, and analogs, and OE-HABP agonists and antagonists as described herein) can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997). The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

15   Tissues that may be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vascular (including vascular endothelium), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis. Additionally, these compounds can be used to treat or prevent cell death (e.g., hematopoietic cell death) during processes of inflammation or tissue injury.

BM-HABP polynucleotides or polypeptides (including BM-HABP fragments, variants, derivatives, and analogs, and BM-HABP agonists and antagonists as described herein) can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997). The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

25   Tissues that may be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vascular (including vascular endothelium), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis. Additionally, these compounds can be used to

treat or prevent cell death (e.g., hematopoietic cell death) during processes of inflammation or tissue injury.

Moreover, full-length WF-HABP polynucleotides or polypeptides (including full-length WF-HABP fragments, variants, derivatives, and analogs, and full-length WF-HABP agonists and antagonists as described herein) may increase regeneration of tissues difficult to heal, such as diabetic ulcers, gangrene lesions, or open-wounds occurring secondary to immune-compromised conditions. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Full-length WF-HABP polynucleotides or polypeptides and/or full-length WF-HABP agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

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Moreover, OE-HABP polynucleotides or polypeptides (including OE-HABP fragments, variants, derivatives, and analogs, and OE-HABP agonists and antagonists as described herein) may increase regeneration of tissues difficult to heal, such as diabetic ulcers, gangrene lesions, or open-wounds occurring secondary to immune-compromised conditions. For example, increased tendon/ligament regeneration would quicken recovery time after damage. OE-HABP polynucleotides or polypeptides and/or OE-HABP agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds

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Moreover, BM-HABP polynucleotides or polypeptides (including BM-HABP fragments, variants, derivatives, and analogs, and BM-HABP agonists and antagonists as described herein) may increase regeneration of tissues difficult to heal, such as diabetic ulcers, gangrene lesions, or open-wounds occurring secondary to immune-compromised conditions. For example, increased tendon/ligament regeneration would quicken recovery time after damage. BM-HABP polynucleotides or polypeptides and/or BM-HABP agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using full-length WF-HABP polynucleotides or polypeptides and/or full-length WF-HABP agonists or antagonists to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the full-length WF-HABP polynucleotides or polypeptides and/or full-length WF-HABP agonists or antagonists. Moreover, the present invention could be used to recruit beneficial cells or cell types to areas of neural tissue damage or injury, particularly cells which either have the endogenous function of protecting such tissue from additional damage, or which are capable of healing the damaged or diseased tissue through the localized secretion of therapeutic peptides.

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diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the WF-HABP polynucleotides or polypeptides and/or WF-HABP agonists or antagonists. Moreover, the present invention could be used to recruit beneficial cells or cell types to areas of neural tissue damage or injury, particularly cells which either have the endogenous function of protecting such tissue from additional damage, or which are capable of healing the damaged or diseased tissue through the localized secretion of therapeutic peptides.

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present invention could be used to recruit beneficial cells or cell types to areas of neural tissue damage or injury, particularly cells which either have the endogenous function of protecting such tissue from additional damage, or which are capable of healing the damaged or diseased tissue through the localized secretion of therapeutic peptides.

5           Given the activities modulated by full-length WF-HABP, it is readily apparent that a substantially altered (increased or decreased) level of expression of full-length WF-HABP in an individual compared to the standard or "normal" level produces pathological conditions such as those described above. It will also be appreciated by one of ordinary skill that the full-length WF-HABP agonists of the invention will exert modulating activities on any of its target cells.  
10       Therefore, it will be appreciated that conditions caused by a decrease in the standard or normal level of full-length WF-HABP mediated activity in an individual, can be treated by administration of full-length WF-HABP polypeptide or an agonist thereof.

          Given the activities modulated by WF-HABP, it is readily apparent that a substantially altered (increased or decreased) level of expression of WF-HABP in an individual compared to  
15       the standard or "normal" level produces pathological conditions such as those described above. It will also be appreciated by one of ordinary skill that the WF-HABP agonists of the invention will exert modulating activities on any of its target cells. Therefore, it will be appreciated that conditions caused by a decrease in the standard or normal level of WF-HABP mediated activity in an individual, can be treated by administration of WF-HABP polypeptide or an agonist  
20       thereof.

          Given the activities modulated by OE-HABP, it is readily apparent that a substantially altered (increased or decreased) level of expression of OE-HABP in an individual compared to the standard or "normal" level produces pathological conditions such as those described above. It will also be appreciated by one of ordinary skill that the OE-HABP agonists of the invention  
25       will exert modulating activities on any of its target cells. Therefore, it will be appreciated that conditions caused by a decrease in the standard or normal level of OE-HABP mediated activity in an individual, can be treated by administration of OE-HABP polypeptide or an agonist thereof.

          Given the activities modulated by BM-HABP, it is readily apparent that a substantially  
30       altered (increased or decreased) level of expression of BM-HABP in an individual compared to the standard or "normal" level produces pathological conditions such as those described above. It will also be appreciated by one of ordinary skill that the BM-HABP agonists of the invention will exert modulating activities on any of its target cells. Therefore, it will be appreciated that

conditions caused by a decrease in the standard or normal level of BM-HABP mediated activity in an individual, can be treated by administration of BM-HABP polypeptide or an agonist thereof.

Thus, in one embodiment, the present invention is directed to a method for enhancing (i.e., increasing) full-length WF-HABP mediated activity (e.g., cellular proliferation, cellular migration, cellular targeting, metastasis) which involves administering to an individual in need of an increased level of full-length WF-HABP mediated activity, a therapeutically effective amount of full-length WF-HABP polypeptide, fragment, variant, derivative, or analog, or an agonist capable of increasing full-length WF-HABP mediated activity. In specific embodiments, full-length WF-HABP mediated adhesion is increased to treat a disease or condition wherein decreased cell survival, secretion, proliferation, migration, and/or differentiation is exhibited.

Thus, in one embodiment, the present invention is directed to a method for enhancing (i.e., increasing) WF-HABP mediated activity (e.g., cellular proliferation, cellular migration, cellular targeting, metastasis) which involves administering to an individual in need of an increased level of WF-HABP mediated activity, a therapeutically effective amount of WF-HABP polypeptide, fragment, variant, derivative, or analog, or an agonist capable of increasing WF-HABP mediated activity. In specific embodiments, WF-HABP mediated adhesion is increased to treat a disease or condition wherein decreased cell survival, secretion, proliferation, migration, and/or differentiation is exhibited.

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Thus, in one embodiment, the present invention is directed to a method for enhancing (i.e., increasing) BM-HABP mediated activity (e.g., cellular proliferation, cellular migration, cellular targeting, metastasis) which involves administering to an individual in need of an increased level of BM-HABP mediated activity, a therapeutically effective amount of BM-HABP polypeptide, fragment, variant, derivative, or analog, or an agonist capable of



increasing BM-HABP mediated activity. In specific embodiments, BM-HABP mediated adhesion is increased to treat a disease or condition wherein decreased cell survival, secretion, proliferation, migration, and/or differentiation is exhibited.

5 In another embodiment, the present invention is directed to a method for suppressing (i.e., decreasing) full-length WF-HABP mediated activity (e.g., adhesion, rheological properties, water homeostasis, molecular exclusion), which involves administering to an individual in need of a decreased level of full-length WF-HABP mediated activity, a therapeutically effective amount of full-length WF-HABP polypeptide, fragment, variant, derivative, or analog or an antagonist capable of decreasing full-length WF-HABP mediated  
10 activity. In specific embodiments, full-length WF-HABP mediated adhesion is decreased to treat a disease or condition wherein increased cell survival, secretion, proliferation, migration and/or differentiation is exhibited.

15 In another embodiment, the present invention is directed to a method for suppressing (i.e., decreasing) WF-HABP mediated activity (e.g., adhesion, rheological properties, water homeostasis, molecular exclusion), which involves administering to an individual in need of a decreased level of WF-HABP mediated activity, a therapeutically effective amount of WF-HABP polypeptide, fragment, variant, derivative, or analog or an antagonist capable of decreasing WF-HABP mediated activity. In specific embodiments, WF-HABP mediated adhesion is decreased to treat a disease or condition wherein increased cell survival, secretion,  
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25 In another embodiment, the present invention is directed to a method for suppressing (i.e., decreasing) OE-HABP mediated activity (e.g., adhesion, rheological properties, water homeostasis, molecular exclusion), which involves administering to an individual in need of a decreased level of OE-HABP mediated activity, a therapeutically effective amount of OE-HABP polypeptide, fragment, variant, derivative, or analog or an antagonist capable of decreasing OE-HABP mediated activity. In specific embodiments, OE-HABP mediated adhesion is decreased to treat a disease or condition wherein increased cell survival, secretion, proliferation, migration and/or differentiation is exhibited.

30 In another embodiment, the present invention is directed to a method for suppressing (i.e., decreasing) BM-HABP mediated activity (e.g., adhesion, rheological properties, water homeostasis, molecular exclusion), which involves administering to an individual in need of a decreased level of BM-HABP mediated activity, a therapeutically effective amount of BM-HABP polypeptide, fragment, variant, derivative, or analog or an antagonist capable of

decreasing BM-HABP mediated activity. In specific embodiments, BM-HABP mediated adhesion is decreased to treat a disease or condition wherein increased cell survival, secretion, proliferation, migration and/or differentiation is exhibited.

In addition to treating diseases associated with elevated or decreased levels of full-length WF-HABP mediated activity, the invention encompasses methods of administering full-length WF-HABP agonists or antagonists to elevate or reduce full-length WF-HABP mediated biological activity, respectively.

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In addition to treating diseases associated with elevated or decreased levels of BM-HABP mediated activity, the invention encompasses methods of administering BM-HABP agonists or antagonists to elevate or reduce BM-HABP mediated biological activity, respectively.

For example, any method which elevates full-length WF-HABP concentration and/or activity can be used to stimulate hematopoiesis. Using these methods, the full-length WF-HABP polypeptide and nucleotide sequences and full-length WF-HABP agonists as described herein may be used to stimulate hematopoiesis. In a specific embodiment, full-length WF-HABP polypeptides and polynucleotides and/or full-length WF-HABP agonists are used in erythropoietin therapy, which is directed toward supplementing the oxygen carrying capacity of blood. Full-length WF-HABP treatment within the scope of the invention includes, but is not limited, to patients generally requiring blood transfusions, such as, for example, trauma victims, surgical patients, dialysis patients, and patients with a variety of blood composition-affecting disorders, such as hemophilia, cystic fibrosis, pregnancy, menstrual disorders, early anemia of prematurity, spinal cord injury, space flight, aging, various neoplastic disease states, and the like. Examples of patient conditions that require supplementation of the oxygen carrying capacity of blood and which are within the scope of this invention, include but are not limited to: treatment of blood disorders characterized by low or defective red blood cell

production, anemia associated with chronic renal failure, stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis, and increasing levels of hematocrit in vertebrates. The invention also provides for treatment to enhance the oxygen-carrying capacity of an individual, such as for example, an individual encountering hypoxic environmental conditions.

For example, any method which elevates WF-HABP concentration and/or activity can be used to stimulate hematopoiesis. Using these methods, the WF-HABP polypeptide and nucleotide sequences and WF-HABP agonists as described herein may be used to stimulate hematopoiesis. In a specific embodiment, WF-HABP polypeptides and polynucleotides and/or WF-HABP agonists are used in erythropoietin therapy, which is directed toward supplementing the oxygen carrying capacity of blood. WF-HABP treatment within the scope of the invention includes, but is not limited, to patients generally requiring blood transfusions, such as, for example, trauma victims, surgical patients, dialysis patients, and patients with a variety of blood composition-affecting disorders, such as hemophilia, cystic fibrosis, pregnancy, menstrual disorders, early anemia of prematurity, spinal cord injury, space flight, aging, various neoplastic disease states, and the like. Examples of patient conditions that require supplementation of the oxygen carrying capacity of blood and which are within the scope of this invention, include but are not limited to: treatment of blood disorders characterized by low or defective red blood cell production, anemia associated with chronic renal failure, stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis, and increasing levels of hematocrit in vertebrates. The invention also provides for treatment to enhance the oxygen-carrying capacity of an individual, such as for example, an individual encountering hypoxic environmental conditions.

For example, any method which elevates OE-HABP concentration and/or activity can be used to stimulate hematopoiesis. Using these methods, the OE-HABP polypeptide and nucleotide sequences and OE-HABP agonists as described herein may be used to stimulate hematopoiesis. In a specific embodiment, OE-HABP polypeptides and polynucleotides and/or OE-HABP agonists are used in erythropoietin therapy, which is directed toward supplementing the oxygen carrying capacity of blood. OE-HABP treatment within the scope of the invention includes, but is not limited, to patients generally requiring blood transfusions, such as, for example, trauma victims, surgical patients, dialysis patients, and patients with a

variety of blood composition-affecting disorders, such as hemophilia, cystic fibrosis, pregnancy, menstrual disorders, early anemia of prematurity, spinal cord injury, space flight, aging, various neoplastic disease states, and the like. Examples of patient conditions that require supplementation of the oxygen carrying capacity of blood and which are within the scope of this invention, include but are not limited to: treatment of blood disorders characterized by low or defective red blood cell production, anemia associated with chronic renal failure, stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis, and increasing levels of hematocrit in vertebrates. The invention also provides for treatment to enhance the oxygen-carrying capacity of an individual, such as for example, an individual encountering hypoxic environmental conditions.

For example, any method which elevates BM-HABP concentration and/or activity can be used to stimulate hematopoiesis. Using these methods, the BM-HABP polypeptide and nucleotide sequences and BM-HABP agonists as described herein may be used to stimulate hematopoiesis. In a specific embodiment, BM-HABP polypeptides and polynucleotides and/or BM-HABP agonists are used in erythropoietin therapy, which is directed toward supplementing the oxygen carrying capacity of blood. BM-HABP treatment within the scope of the invention includes, but is not limited, to patients generally requiring blood transfusions, such as, for example, trauma victims, surgical patients, dialysis patients, and patients with a variety of blood composition-affecting disorders, such as hemophilia, cystic fibrosis, pregnancy, menstrual disorders, early anemia of prematurity, spinal cord injury, space flight, aging, various neoplastic disease states, and the like. Examples of patient conditions that require supplementation of the oxygen carrying capacity of blood and which are within the scope of this invention, include but are not limited to: treatment of blood disorders characterized by low or defective red blood cell production, anemia associated with chronic renal failure, stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis, and increasing levels of hematocrit in vertebrates. The invention also provides for treatment to enhance the oxygen-carrying capacity of an individual, such as for example, an individual encountering hypoxic environmental conditions.

The invention also encompasses combining the full-length WF-HABP polypeptides and polynucleotides and/or full-length WF-HABP agonists described herein with other proposed or conventional hematopoietic therapies. Thus, for example, full-length WF-HABP agonists can

be combined with compounds that singly exhibit erythropoietic stimulatory effects, such as erythropoietin, testosterone, progenitor cell stimulators, insulin-like growth factor, prostaglandins, serotonin, cyclic AMP, prolactin, and triiodothyronine. Also encompassed are combinations with compounds generally used to treat aplastic anemia, such as methenolene, stanozolol, and nandrolone; to treat iron-deficiency anemia, such as iron preparations; to treat malignant anemia, such as vitamin B12 and/or folic acid; and to treat hemolytic anemia, such as adrenocortical steroids, e.g., corticoids. See e.g., Resegotti et al., *Panminerva Medica*, 23:243-248 (1981); Kurtz, *FEBS Letters*, 14a:105-108 (1982); McGonigle et al., *Kidney Int.*, 25:437-444 (1984); and Pavlovic-Kantera, *Expt. Hematol.*, 8(supp. 8) 283-291 (1980).

The invention also encompasses combining the WF-HABP polypeptides and polynucleotides and/or WF-HABP agonists described herein with other proposed or conventional hematopoietic therapies. Thus, for example, WF-HABP agonists can be combined with compounds that singly exhibit erythropoietic stimulatory effects, such as erythropoietin, testosterone, progenitor cell stimulators, insulin-like growth factor, prostaglandins, serotonin, cyclic AMP, prolactin, and triiodothyronine. Also encompassed are combinations with compounds generally used to treat aplastic anemia, such as methenolene, stanozolol, and nandrolone; to treat iron-deficiency anemia, such as iron preparations; to treat malignant anemia, such as vitamin B12 and/or folic acid; and to treat hemolytic anemia, such as adrenocortical steroids, e.g., corticoids. See e.g., Resegotti et al., *Panminerva Medica*, 23:243-248 (1981); Kurtz, *FEBS Letters*, 14a:105-108 (1982); McGonigle et al., *Kidney Int.*, 25:437-444 (1984); and Pavlovic-Kantera, *Expt. Hematol.*, 8(supp. 8) 283-291 (1980).

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The invention also encompasses combining the BM-HABP polypeptides and polynucleotides and/or BM-HABP agonists described herein with other proposed or conventional hematopoietic therapies. Thus, for example, BM-HABP agonists can be combined with compounds that singly exhibit erythropoietic stimulatory effects, such as erythropoietin, testosterone, progenitor cell stimulators, insulin-like growth factor, prostaglandins, serotonin, cyclic AMP, prolactin, and triiodothyronine. Also encompassed are combinations with compounds generally used to treat aplastic anemia, such as methenolene, stanozolol, and nandrolone; to treat iron-deficiency anemia, such as iron preparations; to treat malignant anemia, such as vitamin B12 and/or folic acid; and to treat hemolytic anemia, such as adrenocortical steroids, e.g., corticoids. See e.g., Resegotti et al., *Panminerva Medica*, 23:243-248 (1981); Kurtz, *FEBS Letters*, 14a:105-108 (1982); McGonigle et al., *Kidney Int.*, 25:437-444 (1984); and Pavlovic-Kantera, *Expt. Hematol.*, 8(supp. 8) 283-291 (1980).

Methods for stimulating hematopoiesis comprise administering a hematopoietically effective amount (i.e., an amount which effects the formation of blood cells) of a pharmaceutical composition containing full-length WF-HABP or a full-length WF-HABP agonist to a patient. The full-length WF-HABP or full-length WF-HABP agonist is administered to the patient by any suitable technique, including but not limited to, parenteral, sublingual, topical, intrapulmonary and intranasal, and those techniques further discussed herein. The pharmaceutical composition optionally contains one or more members of the group consisting of erythropoietin, testosterone, progenitor cell stimulators, insulin-like growth factor, prostaglandins, serotonin, cyclic AMP, prolactin, triiodothyronine, methenolene, stanozolol, and nandrolone, iron preparations, vitamin B12, folic acid and/or adrenocortical steroids. The full-length WF-HABP or full-length WF-HABP agonist and cotreatment drug(s) are suitably delivered by separate or by the same administration route, and at the same or at different times, depending, e.g., on dosing, the clinical condition of the patient, etc.

Methods for stimulating hematopoiesis comprise administering a hematopoietically effective amount (i.e., an amount which effects the formation of blood cells) of a pharmaceutical composition containing WF-HABP or a WF-HABP agonist to a patient. The WF-HABP or WF-HABP agonist is administered to the patient by any suitable technique, including but not limited to, parenteral, sublingual, topical, intrapulmonary and intranasal, and those techniques further discussed herein. The pharmaceutical composition optionally contains one or more members of the group consisting of erythropoietin, testosterone, progenitor cell stimulators, insulin-like growth factor, prostaglandins, serotonin, cyclic AMP, prolactin, triiodothyronine,

methenolene, stanozolol, and nandrolone, iron preparations, vitamin B12, folic acid and/or adrenocortical steroids. The WF-HABP or WF-HABP agonist and cotreatment drug(s) are suitably delivered by separate or by the same administration route, and at the same or at different times, depending, e.g., on dosing, the clinical condition of the patient, etc.

- 5           Methods for stimulating hematopoiesis comprise administering a hematopoietically effective amount (i.e, an amount which effects the formation of blood cells) of a pharmaceutical composition containing OE-HABP or a OE-HABP agonist to a patient. The OE-HABP or OE-HABP agonist is administered to the patient by any suitable technique, including but not limited to, parenteral, sublingual, topical, intrapulmonary and intranasal, and those techniques further
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- 15       suitably delivered by separate or by the same administration route, and at the same or at different times, depending, e.g., on dosing, the clinical condition of the patient, etc.

- Methods for stimulating hematopoiesis comprise administering a hematopoietically effective amount (i.e, an amount which effects the formation of blood cells) of a pharmaceutical composition containing BM-HABP or a BM-HABP agonist to a patient. The BM-HABP or
- 20       BM-HABP agonist is administered to the patient by any suitable technique, including but not limited to, parenteral, sublingual, topical, intrapulmonary and intranasal, and those techniques further discussed herein. The pharmaceutical composition optionally contains one or more members of the group consisting of erythropoietin, testosterone, progenitor cell stimulators, insulin-like growth factor, prostaglandins, serotonin, cyclic AMP, prolactin, triiodothyronine,
- 25       methenolene, stanozolol, and nandrolone, iron preparations, vitamin B12, folic acid and/or adrenocortical steroids. The BM-HABP or BM-HABP agonist and cotreatment drug(s) are suitably delivered by separate or by the same administration route, and at the same or at different times, depending, e.g., on dosing, the clinical condition of the patient, etc.

- For treating abnormal conditions related to an under-expression of full-length WF-HABP
- 30       and its activity, or in which elevated or decreased levels of full-length WF-HABP are desired, several approaches are available. One approach comprises administering to an individual in need of an increased level of full-length WF-HABP mediated activity in the body, a therapeutically effective amount of an isolated full-length WF-HABP polypeptide, fragment,

variant, derivative or analog of the invention, or a compound which activates full-length WF-HABP, i.e., an agonist as described above, optionally in combination with a pharmaceutically acceptable carrier. Alternatively, gene therapy may be employed to effect the endogenous production of full-length WF-HABP by the relevant cells in the subject. For example, a

5 polynucleotide of the invention may be engineered for expression in a replication defective retroviral vector using techniques known in the art. The retroviral expression construct may then be isolated and introduced into a packaging cell transduced with a retroviral plasmid vector containing RNA encoding a polypeptide of the present invention such that the packaging cell now produces infectious viral particles containing the gene of interest. These producer cells

10 may be administered to a subject for engineering cells *in vivo* and expression of the polypeptide *in vivo*. For an overview of gene therapy, see Chapter 20, Gene Therapy and other Molecular Genetic-based Therapeutic Approaches, (and references cited therein) in Human Molecular Genetics, T Strachan and A P Read, BIOS Scientific Publishers Ltd (1996).

For treating abnormal conditions related to an under-expression of OE-HABP and its

15 activity, or in which elevated or decreased levels of OE-HABP are desired, several approaches are available. One approach comprises administering to an individual in need of an increased level of OE-HABP mediated activity in the body, a therapeutically effective amount of an isolated OE-HABP polypeptide, fragment, variant, derivative or analog of the invention, or a compound which activates OE-HABP, i.e., an agonist as described above, optionally in

20 combination with a pharmaceutically acceptable carrier. Alternatively, gene therapy may be employed to effect the endogenous production of OE-HABP by the relevant cells in the subject. For example, a polynucleotide of the invention may be engineered for expression in a replication defective retroviral vector using techniques known in the art. The retroviral expression construct may then be isolated and introduced into a packaging cell transduced with

25 a retroviral plasmid vector containing RNA encoding a polypeptide of the present invention such that the packaging cell now produces infectious viral particles containing the gene of interest. These producer cells may be administered to a subject for engineering cells *in vivo* and expression of the polypeptide *in vivo*. For an overview of gene therapy, see Chapter 20, Gene Therapy and other Molecular Genetic-based Therapeutic Approaches, (and references

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For treating abnormal conditions related to an under-expression of BM-HABP and its activity, or in which elevated or decreased levels of BM-HABP are desired, several approaches



are available. One approach comprises administering to an individual in need of an increased level of BM-HABP mediated activity in the body, a therapeutically effective amount of an isolated BM-HABP polypeptide, fragment, variant, derivative or analog of the invention, or a compound which activates BM-HABP, i.e., an agonist as described above, optionally in combination with a pharmaceutically acceptable carrier. Alternatively, gene therapy may be employed to effect the endogenous production of BM-HABP by the relevant cells in the subject. For example, a polynucleotide of the invention may be engineered for expression in a replication defective retroviral vector using techniques known in the art. The retroviral expression construct may then be isolated and introduced into a packaging cell transduced with a retroviral plasmid vector containing RNA encoding a polypeptide of the present invention such that the packaging cell now produces infectious viral particles containing the gene of interest. These producer cells may be administered to a subject for engineering cells *in vivo* and expression of the polypeptide *in vivo*. For an overview of gene therapy, see Chapter 20, Gene Therapy and other Molecular Genetic-based Therapeutic Approaches, (and references cited therein) in Human Molecular Genetics, T Strachan and A P Read, BIOS Scientific Publishers Ltd (1996).

Further, treatment can be administered, for example, in the form of gene replacement therapy. Specifically, one or more copies of a full-length WF-HABP nucleotide sequence of the invention that directs the production of a full-length WF-HABP gene product exhibiting normal function, may be inserted into the appropriate cells within a patient or animal subject, using vectors which include, but are not limited to, adenovirus, adeno-associated virus, retrovirus and herpesvirus vectors, in addition to other particles that introduce DNA into cells, such as liposomes and gene activated matrices. Because the full-length WF-HABP gene is expressed in hematopoietic tissue, lymph, bone, peripheral blood leukocytes etc, such gene replacement techniques should be capable of delivering full-length WF-HABP gene sequence to these cells within patients, or, alternatively, should involve direct administration of such full-length WF-HABP polynucleotide sequences to the site of the cells in which the full-length WF-HABP gene sequences are to be expressed. Alternatively, targeted homologous recombination can be utilized to correct the defective endogenous full-length WF-HABP gene and/or regulatory sequences thereof (e.g., promoter and enhancer sequences), or alternatively, to "turn on" other dormant full-length WF-HABP activity in the appropriate tissue or cell type.

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Further, treatment can be administered, for example, in the form of gene replacement therapy. Specifically, one or more copies of a OE-HABP nucleotide sequence of the invention that directs the production of a OE-HABP gene product exhibiting normal function, may be inserted into the appropriate cells within a patient or animal subject, using vectors which include, but are not limited to, adenovirus, adeno-associated virus, retrovirus and herpesvirus vectors, in addition to other particles that introduce DNA into cells, such as liposomes and gene activated matrices. Because the OE-HABP gene is expressed in hematopoietic tissue, lymph, bone, peripheral blood leukocytes etc, such gene replacement techniques should be capable of delivering OE-HABP gene sequence to these cells within patients, or, alternatively, should involve direct administration of such OE-HABP polynucleotide sequences to the site of the cells in which the OE-HABP gene sequences are to be expressed. Alternatively, targeted homologous recombination can be utilized to correct the defective endogenous OE-HABP gene and/or regulatory sequences thereof (e.g., promoter and enhancer sequences), or alternatively, to "turn on" other dormant OE-HABP activity in the appropriate tissue or cell type.

Further, treatment can be administered, for example, in the form of gene replacement therapy. Specifically, one or more copies of a BM-HABP nucleotide sequence of the invention that directs the production of a BM-HABP gene product exhibiting normal function, may be inserted into the appropriate cells within a patient or animal subject, using vectors which include, but are not limited to, adenovirus, adeno-associated virus, retrovirus and herpesvirus vectors, in addition to other particles that introduce DNA into cells, such as liposomes and gene activated matrices. Because the BM-HABP gene is expressed in hematopoietic tissue, lymph,

bone, peripheral blood leukocytes etc, such gene replacement techniques should be capable of delivering BM-HABP gene sequence to these cells within patients, or, alternatively, should involve direct administration of such BM-HABP polynucleotide sequences to the site of the cells in which the BM-HABP gene sequences are to be expressed. Alternatively, targeted homologous recombination can be utilized to correct the defective endogenous BM-HABP gene and/or regulatory sequences thereof (e.g., promoter and enhancer sequences), or alternatively, to "turn on" other dormant BM-HABP activity in the appropriate tissue or cell type.

Additional methods which may be utilized to increase the overall level of full-length WF-HABP expression and/or full-length WF-HABP activity include the introduction of appropriate full-length WF-HABP-expressing cells, preferably autologous cells, into a patient at positions and in numbers which are sufficient to ameliorate the symptoms of abnormalities in cell growth regulation, cell signaling, and other full-length WF-HABP mediated activities. Such cells may be either recombinant or non-recombinant. Among the cells which can be administered to increase the overall level of full-length WF-HABP gene expression in a patient are normal cells, which express the full-length WF-HABP gene. Cell-based gene therapy techniques are well known to those skilled in the art, see, e.g., Anderson et al., U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959.

Additional methods which may be utilized to increase the overall level of WF-HABP expression and/or WF-HABP activity include the introduction of appropriate WF-HABP-expressing cells, preferably autologous cells, into a patient at positions and in numbers which are sufficient to ameliorate the symptoms of abnormalities in cell growth regulation, cell signaling, and other WF-HABP mediated activities. Such cells may be either recombinant or non-recombinant. Among the cells which can be administered to increase the overall level of WF-HABP gene expression in a patient are normal cells, which express the WF-HABP gene. Cell-based gene therapy techniques are well known to those skilled in the art, see, e.g., Anderson et al., U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959.

Additional methods which may be utilized to increase the overall level of OE-HABP expression and/or OE-HABP activity include the introduction of appropriate OE-HABP-expressing cells, preferably autologous cells, into a patient at positions and in numbers which are sufficient to ameliorate the symptoms of abnormalities in cell growth regulation, cell signaling, and other OE-HABP mediated activities. Such cells may be either recombinant or non-recombinant. Among the cells which can be administered to increase the overall level of

OE-HABP gene expression in a patient are normal cells, which express the OE-HABP gene. Cell-based gene therapy techniques are well known to those skilled in the art, see, e.g., Anderson et al., U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959.

5 Additional methods which may be utilized to increase the overall level of BM-HABP expression and/or BM-HABP activity include the introduction of appropriate BM-HABP-expressing cells, preferably autologous cells, into a patient at positions and in numbers which are sufficient to ameliorate the symptoms of abnormalities in cell growth regulation, cell  
10 signaling, and other BM-HABP mediated activities. Such cells may be either recombinant or non-recombinant. Among the cells which can be administered to increase the overall level of BM-HABP gene expression in a patient are normal cells, which express the BM-HABP gene. Cell-based gene therapy techniques are well known to those skilled in the art, see, e.g., Anderson et al., U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959.

15 Thus, one embodiment of the invention comprises administering to an individual in need of an increased level of full-length WF-HABP mediated activity compound that stimulates full-length WF-HABP mediated activity (agonist), such as for example, an antibody or full-length WF-HABP fragment, variant, derivative or analog of the invention, along with a pharmaceutically acceptable carrier in an amount effective to enhance (i.e., increase) full-length  
20 WF-HABP mediated activity.

Thus, one embodiment of the invention comprises administering to an individual in need of an increased level of WF-HABP mediated activity compound that stimulates WF-HABP mediated activity (agonist), such as for example, an antibody or WF-HABP fragment, variant, derivative or analog of the invention, along with a pharmaceutically acceptable carrier  
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Thus, one embodiment of the invention comprises administering to an individual in need of an increased level of BM-HABP mediated activity compound that stimulates BM-HABP mediated activity (agonist), such as for example, an antibody or BM-HABP fragment,

variant, derivative or analog of the invention, along with a pharmaceutically acceptable carrier in an amount effective to enhance (i.e., increase) BM-HABP mediated activity.

If the activity of full-length WF-HABP is in excess, several approaches are available to reduce or inhibit full-length WF-HABP activity using molecules derived from the polypeptide and polynucleotide sequences described above. Accordingly, a further aspect of the invention is related to a method for treating an individual in need of a decreased level of full-length WF-HABP mediated activity in the body comprising, administering to such an individual a composition comprising a therapeutically effective amount of a full-length WF-HABP polypeptide, fragment, variant, derivative or analog of the invention which acts as a full-length WF-HABP antagonist or full-length WF-HABP antagonist identified using the methods described herein, optionally, in combination with a pharmaceutically acceptable carrier. Preferably, full-length WF-HABP activity is decreased to treat a disease wherein increased cell survival, secretion, proliferation, migration, and/or differentiation is exhibited. Polypeptides, derivatives, variants and analogs of the invention and other compounds which function as antagonists of full-length WF-HABP can routinely be identified using the assays described *infra* and other techniques known in the art. Preferred antagonists for use in the present invention are full-length WF-HABP-specific antibodies.

If the activity of WF-HABP is in excess, several approaches are available to reduce or inhibit WF-HABP activity using molecules derived from the polypeptide and polynucleotide sequences described above. Accordingly, a further aspect of the invention is related to a method for treating an individual in need of a decreased level of WF-HABP mediated activity in the body comprising, administering to such an individual a composition comprising a therapeutically effective amount of a WF-HABP polypeptide, fragment, variant, derivative or analog of the invention which acts as a WF-HABP antagonist or WF-HABP antagonist identified using the methods described herein, optionally, in combination with a pharmaceutically acceptable carrier. Preferably, WF-HABP activity is decreased to treat a disease wherein increased cell survival, secretion, proliferation, migration, and/or differentiation is exhibited. Polypeptides, derivatives, variants and analogs of the invention and other compounds which function as antagonists of WF-HABP can routinely be identified using the assays described *infra* and other techniques known in the art. Preferred antagonists for use in the present invention are WF-HABP-specific antibodies.

If the activity of OE-HABP is in excess, several approaches are available to reduce or inhibit OE-HABP activity using molecules derived from the polypeptide and polynucleotide

sequences described above. Accordingly, a further aspect of the invention is related to a method for treating an individual in need of a decreased level of OE-HABP mediated activity in the body comprising, administering to such an individual a composition comprising a therapeutically effective amount of a OE-HABP polypeptide, fragment, variant, derivative or analog of the invention which acts as a OE-HABP antagonist or OE-HABP antagonist identified using the methods described herein, optionally, in combination with a pharmaceutically acceptable carrier. Preferably, OE-HABP activity is decreased to treat a disease wherein increased cell survival, secretion, proliferation, migration, and/or differentiation is exhibited. Polypeptides, derivatives, variants and analogs of the invention and other compounds which function as antagonists of OE-HABP can routinely be identified using the assays described *infra* and other techniques known in the art. Preferred antagonists for use in the present invention are OE-HABP-specific antibodies.

If the activity of BM-HABP is in excess, several approaches are available to reduce or inhibit BM-HABP activity using molecules derived from the polypeptide and polynucleotide sequences described above. Accordingly, a further aspect of the invention is related to a method for treating an individual in need of a decreased level of BM-HABP mediated activity in the body comprising, administering to such an individual a composition comprising a therapeutically effective amount of a BM-HABP polypeptide, fragment, variant, derivative or analog of the invention which acts as a BM-HABP antagonist or BM-HABP antagonist identified using the methods described herein, optionally, in combination with a pharmaceutically acceptable carrier. Preferably, BM-HABP activity is decreased to treat a disease wherein increased cell survival, secretion, proliferation, migration, and/or differentiation is exhibited. Polypeptides, derivatives, variants and analogs of the invention and other compounds which function as antagonists of BM-HABP can routinely be identified using the assays described *infra* and other techniques known in the art. Preferred antagonists for use in the present invention are BM-HABP-specific antibodies.

In another approach, full-length WF-HABP activity can be reduced or inhibited by decreasing the level of full-length WF-HABP gene expression. In one embodiment, this is accomplished through the use of antisense sequences, either internally generated or separately administered (see, for example, O'Connor, J. Neurochem. (1991) 56:560 in Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA or through triple-helix formation. Antisense techniques are discussed, for

example, in Okano, J. *Neurochem.* 56:560 (1991); *Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression*, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., *Nucleic Acids Research* 6:3073 (1979); Cooney et al., *Science* 241:456 (1988); and Dervan et al., *Science* 251:1360 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA. For example, the 5' coding portion of a polynucleotide that encodes full-length WF-HABP polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the full-length WF-HABP polypeptide. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into polypeptide.

In another approach, WF-HABP activity can be reduced or inhibited by decreasing the level of WF-HABP gene expression. In one embodiment, this is accomplished through the use of antisense sequences, either internally generated or separately administered (see, for example, O'Connor, J. *Neurochem.* (1991) 56:560 in *Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression*, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA or through triple-helix formation. Antisense techniques are discussed, for example, in Okano, J. *Neurochem.* 56:560 (1991); *Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression*, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., *Nucleic Acids Research* 6:3073 (1979); Cooney et al., *Science* 241:456 (1988); and Dervan et al., *Science* 251:1360 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA. For example, the 5' coding portion of a polynucleotide that encodes WF-HABP polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the WF-HABP polypeptide. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into polypeptide.

In another approach, OE-HABP activity can be reduced or inhibited by decreasing the level of OE-HABP gene expression. In one embodiment, this is accomplished through the use of antisense sequences, either internally generated or separately administered (see, for example, O'Connor, J. *Neurochem.* (1991) 56:560 in *Oligodeoxynucleotides as Antisense Inhibitors of*

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In another approach, BM-HABP activity can be reduced or inhibited by decreasing the level of BM-HABP gene expression. In one embodiment, this is accomplished through the use of antisense sequences, either internally generated or separately administered (see, for example, O'Connor, J. *Neurochem.* (1991) 56:560 in *Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression*, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA or through triple-helix formation. Antisense techniques are discussed, for example, in Okano, J. *Neurochem.* 56:560 (1991); *Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression*, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., *Nucleic Acids Research* 6:3073 (1979); Cooney et al., *Science* 241:456 (1988); and Dervan et al., *Science* 251:1360 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA. For example, the 5' coding portion of a polynucleotide that encodes BM-HABP polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the BM-HABP polypeptide. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into polypeptide.



In one embodiment, the full-length WF-HABP antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the full-length WF-HABP antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding full-length WF-HABP, or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, Nature 29:304-310 (1981), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., Cell 22:787-797 (1980)), the herpes thymidine promoter (Wagner et al., Proc. Natl. Acad. Sci. U.S.A. 78:1441-1445 (1981)), the regulatory sequences of the metallothionein gene (Brinster et al., Nature 296:39-42 (1982)), etc.

In one embodiment, the WF-HABP antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the WF-HABP antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding WF-HABP, or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, Nature 29:304-310 (1981), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., Cell 22:787-797 (1980)), the herpes thymidine promoter (Wagner et al., Proc. Natl. Acad. Sci. U.S.A. 78:1441-1445 (1981)), the regulatory sequences of the metallothionein gene (Brinster et al., Nature 296:39-42 (1982)), etc.

In one embodiment, the OE-HABP antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the OE-HABP antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding OE-HABP, or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, Nature 29:304-310 (1981)), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., Cell 22:787-797 (1980)), the herpes thymidine promoter (Wagner et al., Proc. Natl. Acad. Sci. U.S.A. 78:1441-1445 (1981)), the regulatory sequences of the metallothionein gene (Brinster et al., Nature 296:39-42 (1982)), etc.

In one embodiment, the BM-HABP antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the BM-HABP antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding BM-HABP, or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, Nature 29:304-310 (1981)), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., Cell 22:787-797 (1980)), the herpes thymidine promoter (Wagner et al., Proc. Natl. Acad. Sci. U.S.A. 78:1441-1445 (1981)), the regulatory sequences of the metallothionein gene (Brinster et al., Nature 296:39-42 (1982)), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a full-length WF-HABP gene. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded full-length WF-HABP antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a full-length WF-HABP RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a WF-HABP gene. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded WF-HABP antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a WF-HABP RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a OE-HABP gene. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded OE-HABP antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a OE-HABP RNA it may contain and

still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

5 The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a BM-HABP gene. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded BM-HABP antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex  
10 formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a BM-HABP RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of  
15 the hybridized complex.

Potential full-length WF-HABP antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al., Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy full-length WF-HABP mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes  
20 cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the  
25 nucleotide sequence of full-length WF-HABP (Figures 1A-H; SEQ ID NO:1). Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the full-length WF-HABP mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts. DNA constructs encoding the ribozyme  
30 may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. Since ribozymes, unlike antisense molecules are catalytic, a lower intracellular concentration is required for efficiency.

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Potential BM-HABP antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al., Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy BM-HABP mRNAs, the use of

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10 numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of BM-HABP (Figures 4A-B; SEQ ID NO:10). Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the BM-HABP mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts. DNA constructs encoding the ribozyme may be introduced into the cell in the same

15 manner as described above for the introduction of antisense encoding DNA. Since ribozymes, unlike antisense molecules are catalytic, a lower intracellular concentration is required for efficiency.

Endogenous full-length WF-HABP gene expression can also be reduced by inactivating or "knocking out" the full-length WF-HABP gene or its promoter using targeted homologous recombination (e.g., see Smithies et al., Nature 317:330-234 (1985); Thomas et al., Cell 51:503-512 (1987); Thompson et al., Cell 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). Such approach can be adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors.

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Alternatively, endogenous full-length WF-HABP gene expression can be reduced by targeted deoxyribonucleotide sequences complementary to the regulatory region of the full-length WF-HABP gene (i.e., the full-length WF-HABP promoter and/or enhancers) to form triple helical structures that prevent transcription of the full-length WF-HABP gene in target cells in the body, see generally, Helene et al., Ann, N.Y. Acad. Sci. 660:27-36 (1992); Helene, C., Anticancer Drug Des., 6(6):569-584 (1991); and Maher, L.J., Bioassays 14(12):807-815 (1992)).

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5           Thus, one embodiment of the invention comprises administering to an individual in need of a decreased level of full-length WF-HABP mediated activity, a full-length WF-HABP inhibitor compound (antagonist), such as for example, an antibody or full-length WF-HABP fragment, variant, derivative or analog of the invention, along with a pharmaceutically acceptable carrier in an amount effective to suppress (i.e., lower) full-length WF-HABP  
10 mediated activity.

          Thus, one embodiment of the invention comprises administering to an individual in need of a decreased level of WF-HABP mediated activity, a WF-HABP inhibitor compound (antagonist), such as for example, an antibody or WF-HABP fragment, variant, derivative or analog of the invention, along with a pharmaceutically acceptable carrier in an amount effective  
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25 to suppress (i.e., lower) BM-HABP mediated activity.

### **Formulation and administration**

          It will be appreciated that conditions caused by a decrease in the standard or normal level of full-length WF-HABP mediated activity in an individual, can be treated by  
30 administration of full-length WF-HABP polypeptide or fragment, variant, derivative, or analog of the invention or an agonist thereof. Thus, the invention further provides a method of treating an individual in need of an increased level of full-length WF-HABP mediated activity comprising administering to such an individual a pharmaceutical composition comprising an



effective amount of an isolated full-length WF-HABP polynucleotide or polypeptide; or fragment, variant, derivative, or analog of the invention, such as for example, the full length form of the full-length WF-HABP encoding polynucleotide, effective to increase the full-length WF-HABP mediated activity level in such an individual.

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10 a pharmaceutical composition comprising an effective amount of an isolated WF-HABP polynucleotide or polypeptide; or fragment, variant, derivative, or analog of the invention, such as for example, the full length form of the WF-HABP encoding polynucleotide, effective to increase the WF-HABP mediated activity level in such an individual.

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25 HABP polypeptide or fragment, variant, derivative, or analog of the invention or an agonist thereof. Thus, the invention further provides a method of treating an individual in need of an increased level of BM-HABP mediated activity comprising administering to such an individual a pharmaceutical composition comprising an effective amount of an isolated BM-HABP polynucleotide or polypeptide; or fragment, variant, derivative, or analog of the invention, such  
30 as for example, the full length form of the BM-HABP encoding polynucleotide, effective to increase the BM-HABP mediated activity level in such an individual.

The dosage range required depends on the choice of peptide, the route of administration, the nature of the formulation, the nature of the subject's condition, and the

judgment of the attending practitioner. As a general proposition, the total pharmaceutically effective amount of full-length WF-HABP polypeptide administered parenterally per dose will be in the range of about 1  $\mu\text{g/kg/day}$  to 10  $\text{mg/kg/day}$  of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01  $\text{mg/kg/day}$ , and most preferably for humans this dose is in the range of 0.1-100  $\text{mg/kg}$  of subject, or between about 0.01 and 1  $\text{mg/kg/day}$ . If given continuously, the full-length WF-HABP polypeptide is typically administered at a dose rate of about 1  $\mu\text{g/kg/hour}$  to about 50  $\mu\text{g/kg/hour}$ , either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. Wide variations in the needed dosage, however, are to be expected in view of the variety of compounds available and the differing efficiencies of various routes of administration. For example, oral administration would be expected to require higher dosages than administration by intravenous injection. Variations in these dosage levels can be adjusted using standard empirical routines for optimization, as is well understood in the art.

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Pharmaceutical compositions containing the full-length WF-HABP polypeptides and polynucleotides of the invention (including fragments, variants, derivatives or analogs), and full-length WF-HABP agonists and antagonists may be routinely formulated in combination with a pharmaceutically acceptable carrier. By "pharmaceutically acceptable carrier" is meant a

non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. In a specific embodiment, "pharmaceutically acceptable" means approved by a regulatory agency of the federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly humans. Nonlimiting examples of suitable pharmaceutical carriers according to this embodiment are provided in "Remington's Pharmaceutical Sciences" by E.W. Martin, and include sterile liquids, such as water, saline, buffered saline, glycerol, ethanol, and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Formulation should suit the mode of administration, and is well within the skill of the art. For example, water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can be employed as liquid carriers, particularly for injectable solutions. The invention additionally relates to pharmaceutical packs and kits comprising one or more containers filled with one or more of the ingredients of the aforementioned compositions of the invention.

Pharmaceutical compositions containing the WF-HABP polypeptides and polynucleotides of the invention (including fragments, variants, derivatives or analogs), and WF-HABP agonists and antagonists may be routinely formulated in combination with a pharmaceutically acceptable carrier. By "pharmaceutically acceptable carrier" is meant a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. In a specific embodiment, "pharmaceutically acceptable" means approved by a regulatory agency of the federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly humans. Nonlimiting examples of suitable pharmaceutical carriers according to this embodiment are provided in "Remington's Pharmaceutical Sciences" by E.W. Martin, and include sterile liquids, such as water, saline, buffered saline, glycerol, ethanol, and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Formulation should suit the mode of administration, and is well within the skill of the art. For example, water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can be employed as liquid carriers, particularly for injectable solutions. The invention additionally relates to pharmaceutical packs and kits comprising one or more

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Polypeptides and other compounds of the present invention may be administered alone or in conjunction with other compounds, such as therapeutic compounds. The pharmaceutical composition of the invention may be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, drops or transdermal patch), buccally, or as an oral or nasal spray. Preferred forms of systemic administration of the pharmaceutical compositions include parenteral injection, typically by intravenous injection. Other injection routes, such as subcutaneous, intramuscular, intrasternal, intraarticular or intraperitoneal, can be used. Alternative means for systemic administration include transmucosal and transdermal administration using penetrants such as bile salts or fusidic acids or other detergents. In addition, if properly formulated in enteric or encapsulated formulations, oral administration may also be possible. Administration of these compounds may also be topical and/or localized, in the form of salves, pastes, gels and the like.

Polypeptides used in treatment can also be generated endogenously in the subject, in treatment modalities often referred to as "gene therapy" as described above. Thus, for example, cells from a subject may be engineered with a polynucleotide, such as a DNA or RNA, to encode a polypeptide ex vivo, and for example, by the use of a retroviral plasmid vector. The cells are then introduced into the subject.

### Gene Mapping

The nucleic acid molecules of the present invention are also valuable for chromosome identification. The sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome. Moreover, there is a current need for identifying particular sites on the chromosome. Few chromosome marking reagents based on actual sequence data (repeat polymorphisms) are presently available for marking chromosomal location. The mapping of DNAs to chromosomes according to the present invention is an important first step in correlating those sequences with genes associated with disease.

In certain preferred embodiments in this regard, the cDNA herein disclosed is used to clone genomic DNA of a full-length WF-HABP gene. This can be accomplished using a variety of well known techniques and libraries, which generally are available commercially. The genomic DNA then is used for *in situ* chromosome mapping using well known techniques for this purpose. The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

In certain preferred embodiments in this regard, the cDNA herein disclosed is used to clone genomic DNA of a WF-HABP gene. This can be accomplished using a variety of well known techniques and libraries, which generally are available commercially. The genomic DNA then is used for *in situ* chromosome mapping using well known techniques for this purpose. The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

In certain preferred embodiments in this regard, the cDNA herein disclosed is used to clone genomic DNA of a OE-HABP gene. This can be accomplished using a variety of well known techniques and libraries, which generally are available commercially. The genomic DNA then is used for *in situ* chromosome mapping using well known techniques for this purpose. The gene encoding the disclosed cDNA is believed to reside on chromosome 15. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 15.

In certain preferred embodiments in this regard, the cDNA herein disclosed is used to clone genomic DNA of a BM-HABP gene. This can be accomplished using a variety of well known techniques and libraries, which generally are available commercially. The genomic DNA then is used for *in situ* chromosome mapping using well known techniques for this purpose.

In addition, in some cases, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the cDNA. Computer analysis of the 3' untranslated region of the gene is used to rapidly select primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Fluorescence *in situ* hybridization ("FISH") of a cDNA clone to a metaphase chromosomal spread can be used to provide a precise chromosomal location in one step. This technique can

be used with probes from the cDNA as short as 50 or 60 bp. For a review of this technique, see Verma *et al.*, *Human Chromosomes: A Manual Of Basic Techniques*, Pergamon Press, New York (1988).

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found, for example, in V. McKusick, *Mendelian Inheritance In Man*, available on-line through Johns Hopkins University, Welch Medical Library. The relationship between genes and diseases that have been mapped to the same chromosomal region are then identified through linkage analysis (coinheritance of physically adjacent genes).

Next, it is necessary to determine the differences in the cDNA or genomic sequence between affected and unaffected individuals. If a mutation is observed in some or all of the affected individuals but not in any normal individuals, then the mutation is likely to be the causative agent of the disease.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting. Thus, the present invention is not to be limited in scope by the specific embodiments described herein, which are intended as single illustrations of individual aspects of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

The entire disclosure of all publications (including patents, patent applications, journal articles, laboratory manuals, books, or other documents) cited herein are hereby incorporated by reference.

Further, the Sequence Listing submitted herewith in paper and computer readable form is herein incorporated by reference in their entireties.



## **Examples**

### **Example 1: Isolation of the WF-HABP, OE-HABP, or BM-HABP cDNA Clone From the Deposited Sample**

5 The cDNA for WF-HABP, OE-HABP, or BM-HABP, OE-HABP, or BM-HABP is inserted into the EcoRI and Xho I multiple cloning site of pBluescript (Stratagene). pBluescript contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. (See, for instance, Gruber, C. E., et al., *Focus* 15:59-10 (1993).)

Two approaches can be used to isolate WF-HABP, OE-HABP, or BM-HABP from the deposited sample. First, a specific polynucleotide of SEQ ID NO:1, 4, 7, or 10 with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with  $^{32}\text{P}$ -g-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., 15 Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents. The transformants are plated on 1.5% agar 20 plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

25 Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:1, 4, 7, or 10 (i.e., within the region of SEQ ID NO:1, 4, 7, or 10 bounded by the 5' NT and the 3' NT of the clone) are synthesized and used to amplify the WF-HABP, OE-HABP, or BM-HABP cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 ul of reaction mixture with 30 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM  $\text{MgCl}_2$ , 0.01% (w/v) gelatin, 20 uM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94 degree C for 1 min; annealing at 55 degree C for 1 min; elongation at 72 degree C for 1 min) are performed

with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

5 Several methods are available for the identification of the 5' or 3' non-coding portions of the WF-HABP, OE-HABP, or BM-HABP gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating  
10 the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the  
15 WF-HABP, OE-HABP, or BM-HABP gene of interest is used to PCR amplify the 5' portion of the WF-HABP, OE-HABP, or BM-HABP full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if  
20 necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

25 This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to  
30 the WF-HABP, OE-HABP, or BM-HABP gene.

**Example 2: Isolation of Full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP Genomic Clones**

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:1, 4, 7, or 10., according to the method described in Example 1. (See also, Sambrook.)

**5     Example 3: Chromosomal Mapping of Full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP**

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:1, 4, 7, or 10. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30  
 10     seconds, 95 degree C; 1 minute, 56 degree C; 1 minute, 70 degree C. This cycle is repeated 32 times followed by one 5 minute cycle at 70 degree C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an  
 15     approximately 100 bp PCR fragment in the particular somatic cell hybrid. For example, the gene encoding the disclosed full-length WF-HABP cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3. Moreover, the gene encoding the disclosed OE-HABP cDNA is believed to reside on chromosome 15. Accordingly, polynucleotides related to this invention  
 20     are useful as a marker in linkage analysis for chromosome 15.

**Example 4: Bacterial Expression of Full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP Protein**

Full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide  
 25     encoding a full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide of the invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the  
 30     expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen Inc, Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp<sup>r</sup>), a bacterial origin of replication (ori), an IPTG-regulatable

promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

Specifically, to clone the full-length WF-HABP polypeptide in a bacterial vector, the 5' primer has the sequence 5'

5 GCAGCAGGATCCATGATGGACCAGGGCTGCCGGGAAATCCTTAC 3' (SEQ ID NO:13) containing the underlined EcoRI restriction site followed by a number of nucleotides of the amino terminal coding sequence of the full-length WF-HABP sequence in SEQ ID NO:1. One of ordinary skill in the art would appreciate, of course, that the point in the protein coding sequence where the 5' primer begins may be varied to amplify a DNA segment encoding any  
10 desired portion of the complete full-length WF-HABP protein shorter or longer than the full-length form of the protein. The 3' primer has the sequence 5' GCAGCATCTAGATCACTTGACTGTGAGGATCCTCTGGGTGTCAG 3' (SEQ ID NO:14) containing the underlined XhoI restriction site followed by a number nucleotides complementary to the 3' end of the coding sequence of the full-length WF-HABP  
15 polynucleotide sequence of SEQ ID NO:1.

Specifically, to clone the WF-HABP polypeptide in a bacterial vector, the 5' primer has the sequence 5'

GCAGCAGGATCCATGGTCACTTGTACCTGCCTGCCCGACTACGAG 3' (SEQ ID NO:15) containing the underlined EcoRI restriction site followed by a number of nucleotides of the amino terminal coding sequence of the WF-HABP sequence in SEQ ID NO:4. One of  
20 ordinary skill in the art would appreciate, of course, that the point in the protein coding sequence where the 5' primer begins may be varied to amplify a DNA segment encoding any desired portion of the complete WF-HABP protein shorter or longer than the full-length form of the protein. The 3' primer has the sequence 5'  
25 GCAGCATCTAGATCACTTGACTGTGAGGATCCTCTGGGTGTCAGG 3' (SEQ ID NO:16) containing the underlined XhoI restriction site followed by a number nucleotides complementary to the 3' end of the coding sequence of the WF-HABP polynucleotide sequence of SEQ ID NO:4.

Specifically, to clone the OE-HABP polypeptide in a bacterial vector, the 5' primer has the sequence 5'

30 GCAGCAGGATCCATGGGCCTGTTGCTCCTGGTCCCATTGCTCCTGCTG 3' (SEQ ID NO:17) containing the underlined EcoRI restriction site followed by a number of nucleotides of the amino terminal coding sequence of the OE-HABP sequence in SEQ ID NO:7 One of

ordinary skill in the art would appreciate, of course, that the point in the protein coding sequence where the 5' primer begins may be varied to amplify a DNA segment encoding any desired portion of the complete OE-HABP protein shorter or longer than the full-length form of the protein. The 3' primer has the sequence 5'

5 GCAGCATCTAGAATTTTCTTGGCAGGCTTCCCTTGCTTNTGTCAG 3' (SEQ ID NO:18) containing the underlined XhoI restriction site followed by a number nucleotides complementary to the 3' end of the coding sequence of the OE-HABP polynucleotide sequence of SEQ ID NO:7.

Specifically, to clone the BM-HABP polypeptide in a bacterial vector, the 5' primer 10 has the sequence 5'

GCAGCAGGATCCATGACAGGCCCGGGCAAGCACAAAGTGTGAGTG 3' (SEQ ID NO:19) containing the underlined EcoRI restriction site followed by a number of nucleotides of

the amino terminal coding sequence of the BM-HABP sequence in SEQ ID NO:10. One of ordinary skill in the art would appreciate, of course, that the point in the protein coding sequence where the 5' primer begins may be varied to amplify a DNA segment encoding any 15 desired portion of the complete BM-HABP protein shorter or longer than the full-length form of the protein. The 3' primer has the sequence 5'

GCAGCATCTAGATCAAAATGNTGGAAGCCGATTGTTTTCCGTTTATCC 3' (SEQ ID NO:20) containing the underlined XhoI restriction site followed by a number nucleotides 20 complementary to the 3' end of the coding sequence of the BM-HABP polynucleotide sequence of SEQ ID NO:10.

The PQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pBluescript vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the *E. coli* strain M15/rep4 (Qiagen, Inc.) which 25 contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan<sup>r</sup>). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in 30 LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.<sup>600</sup>) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside)

is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg).

5 In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide, called pHE4a. (ATCC Accession Number 209645, deposited February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a  
10 T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and KpnI,  
15 BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated  
20 according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

#### 25 **Example 5: Cloning and Expression of Full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP in a Baculovirus Expression System**

In this example, the plasmid shuttle vector pA2 is used to insert full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide into a baculovirus to express insert full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP. This expression vector contains  
30 the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E.*

*coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

Specifically, the full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP cDNA sequence contained in the deposited clone, including the AUG initiation codon and any naturally associated leader sequence, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

More specifically, the cDNA sequence encoding the full-length WF-HABP protein including the AUG initiation codon and the sequence shown in SEQ ID NO:1, is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the gene. The 5' primer has the sequence 5' GCAGCAAGATCTGCCATCATGATGGACCAGGGCTGCCGGGAAATCCTT

AC 3' (SEQ ID NO: 21) containing the BglII restriction enzyme site, an efficient signal for initiation of translation in eukaryotic cells (Kozak, M., *J. Mol. Biol.* 196:947-950 (1987)), followed by a number of nucleotides of the sequence of the complete full-length WF-HABP protein shown in Figures 1A-H (SEQ ID NO:1), beginning with the AUG initiation codon. The 3' primer has the sequence 5' GCAGCATCTAGATCACTTGACTGTGAGGATCCTCTGGGTGTCAGG 3' (SEQ ID NO: 22) containing the XbaI restriction site followed by a number of nucleotides complementary to the 3' noncoding sequence in Figures 1A-H (SEQ ID NO:1).

More specifically, the cDNA sequence encoding the WF-HABP protein of the deposited clone, including the AUG initiation codon and the sequence shown in SEQ ID NO:4,

is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the gene. The 5' primer has the sequence 5' GCAGCAAGATCTGCCATCATGGTCACTTGTACCTGCCTGCCCCGACTACG

AG 3' (SEQ ID NO: 23) containing the BglII restriction enzyme site, an efficient signal for initiation of translation in eukaryotic cells (Kozak, M., *J. Mol. Biol.* 196:947-950 (1987)), followed by a number of nucleotides of the sequence of the complete WF-HABP protein shown in Figures 2A-B (SEQ ID NO:4), beginning with the AUG initiation codon. The 3' primer has the sequence 5' GCAGCATCTAGATCACTTGACTGTGAGGATCCTCTGGGTGTCAGG 3' (SEQ ID NO: 24) containing the XbaI restriction site followed by a number of nucleotides complementary to the 3' noncoding sequence in Figures 2A-B (SEQ ID NO:4).

More specifically, the cDNA sequence encoding the OE-HABP protein of the deposited clone, including the AUG initiation codon and the sequence shown in SEQ ID NO:7, is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the gene. The 5' primer has the sequence 5' GCAGCAAGATCTGCCATCATGGGCCTGTTGCTCCTGGTCCCATTTGCTCC

TGCTG 3' (SEQ ID NO: 25) containing the BglII restriction enzyme site, an efficient signal for initiation of translation in eukaryotic cells (Kozak, M., *J. Mol. Biol.* 196:947-950 (1987)), followed by a number of nucleotides of the sequence of the complete OE-HABP protein shown in Figures 3A-B (SEQ ID NO:7), beginning with the AUG initiation codon. The 3' primer has the sequence 5' GCAGCATCTAGAATTTTCTTGGCAGGCTTCCCTTGCTTNTGTCAG 3' (SEQ ID NO: 26) containing the XbaI restriction site followed by a number of nucleotides complementary to the 3' noncoding sequence in Figures 3A-B (SEQ ID NO:7).

More specifically, the cDNA sequence encoding the BM-HABP protein of the deposited clone, including the AUG initiation codon and the sequence shown in SEQ ID NO:10, is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the gene. The 5' primer has the sequence 5' GCAGCAAGATCTGCCATCATGACAGGCCCGGGCAAGCACAAGTGTGAGTG 3' (SEQ ID NO: 27) containing the BglII restriction enzyme site, an efficient signal for initiation of translation in eukaryotic cells (Kozak, M., *J. Mol. Biol.* 196:947-950 (1987)), followed by a number of nucleotides of the sequence of the complete BM-HABP protein shown in Figures 4A-B (SEQ ID NO:10), beginning with the AUG initiation codon. The 3' primer has the



sequence 5' GCAGCATCTAGATCAAAATGNTGGAAGCCGATTGTTTTCCGGTTTATCC  
3' (SEQ ID NO: 28) containing the XbaI restriction site followed by a number of nucleotides  
complementary to the 3' noncoding sequence in Figures 4A-B (SEQ ID NO:10).

The amplified fragment is isolated from a 1% agarose gel using a commercially  
available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with  
appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can  
be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the  
art. The DNA is then isolated from a 1% agarose gel using a commercially available kit  
("Geneclean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA  
ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning  
Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture  
plates. Bacteria containing the plasmid are identified by digesting DNA from individual  
colonies and analyzing the digestion product by gel electrophoresis. The sequence of the  
cloned fragment is confirmed by DNA sequencing.

Five ug of a plasmid containing the polynucleotide is co-transfected with 1.0 ug of a  
commercially available linearized baculovirus DNA ("BaculoGold® baculovirus DNA",  
Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc.  
Natl. Acad. Sci. USA 84:7413-7417 (1987). One ug of BaculoGold® virus DNA and 5 ug of  
the plasmid are mixed in a sterile well of a microtiter plate containing 50 ul of serum-free  
Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 ul Lipofectin  
plus 90 ul Grace's medium are added, mixed and incubated for 15 minutes at room  
temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL  
1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The  
plate is then incubated for 5 hours at 27 degrees C. The transfection solution is then removed  
from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is  
added. Cultivation is then continued at 27 degrees C for four days.

After four days the supernatant is collected and a plaque assay is performed, as  
described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies  
Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones,  
which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type  
can also be found in the user's guide for insect cell culture and baculovirology distributed by

Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 ul of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells  
 5 seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4 degree C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If  
 10 radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 uCi of <sup>35</sup>S-methionine and 5 uCi <sup>35</sup>S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins are analyzed by SDS-PAGE followed by  
 15 autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide.

#### 20 **Example 6: Expression of Full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP in Mammalian Cells**

Full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence,  
 25 and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV, HIV and the early promoter of the cytomegalovirus (CMV). However, cellular  
 30 elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2DHFR (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and

pCMVSPORT 3.0. Mammalian host cells that could be used include, human HeLa, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide can be expressed in stable cell lines containing the full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., *J. Biol. Chem.* 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., *Biochem. et Biophys. Acta*, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., *Biotechnology* 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., *Biochem J.* 227:277-279 (1991); Bebbington et al., *Bio/Technology* 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-DHFR (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., *Molecular and Cellular Biology*, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., *Cell* 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of WF-HABP, OE-HABP, or BM-HABP. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC4 is digested with BamHI and XbaI and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

The cDNA sequence encoding the full-length WF-HABP protein in the deposited clone is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of

the gene. The 5' primer has the sequence 5' GCAGCAGGATCCGCCATCATGATGGACCAGGGCTGCCGGGAAATCCTTAC 3' (SEQ ID NO:29) containing the BamHI restriction enzyme site, an efficient signal for initiation of translation in eukaryotic cells (Kozak, M., *J. Mol. Biol.* 196:947-950 (1987)), followed by a number of nucleotides of the sequence of the complete full-length WF-HABP protein shown in Figures 1A-H (SEQ ID NO:1), beginning with the AUG initiation codon. The 3' primer has the sequence 5' GCAGCATCTAGATCACTTGACTGTGAGGATCCTCTGGGTGTCAG 3' (SEQ ID NO: 30) containing the XbaI restriction site followed by a number of nucleotides complementary to the 3' noncoding sequence in Figures 1A-H (SEQ ID NO:1).

The cDNA sequence encoding the WF-HABP protein in the deposited clone is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the gene. The 5' primer has the sequence 5' GCAGCAAGATCTGCCATCATGATGGTCACTTGTACCTGCCTGCCCCGACTACGAG 3' (SEQ ID NO: 31) containing the BamHI restriction enzyme site, an efficient signal for initiation of translation in eukaryotic cells (Kozak, M., *J. Mol. Biol.* 196:947-950 (1987)), followed by a number of nucleotides of the sequence of the complete WF-HABP protein shown in Figures 2A-B (SEQ ID NO:4), beginning with the AUG initiation codon. The 3' primer has the sequence 5' GCAGCATCTAGATCACTTGACTGTGAGGATCCTCTGGGTGTCAGG 3' (SEQ ID NO: 32) containing the XbaI restriction site followed by a number of nucleotides complementary to the 3' noncoding sequence in Figures 2A-B (SEQ ID NO:4).

The cDNA sequence encoding the OE-HABP protein in the deposited clone is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the gene. The 5' primer has the sequence 5' GCAGCAAGATCTGCCATCATGGGCCTGTTGCTCCTGGTCCCATTGCTCCTGCTG 3' (SEQ ID NO: 33) containing the BamHI restriction enzyme site, an efficient signal for initiation of translation in eukaryotic cells (Kozak, M., *J. Mol. Biol.* 196:947-950 (1987)), followed by a number of nucleotides of the sequence of the complete OE-HABP protein shown in Figures 3A-B (SEQ ID NO:7), beginning with the AUG initiation codon. The 3' primer has the sequence 5' GCAGCATCTAGAATTTTCTTGGCAGGCTTCCTTGCTTNTGTCAG 3' (SEQ ID NO: 34) containing the XbaI restriction site followed by a number of nucleotides complementary to the 3' noncoding sequence in Figures 3A-B (SEQ ID NO:7).

The cDNA sequence encoding the BM-HABP protein in the deposited clone is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the

gene. The 5' primer has the sequence 5' GCAGCAAGATCTGCCATCATGACAGGCCCGGGCAAGCACAAGTGTGAGTG 3' (SEQ ID NO: 35) containing the BamHI restriction enzyme site, an efficient signal for initiation of translation in eukaryotic cells (Kozak, M., *J. Mol. Biol.* 196:947-950 (1987)), followed by a number of nucleotides of the sequence of the complete OE-HABP protein shown in Figures 4A-B (SEQ ID NO:10), beginning with the AUG initiation codon. The 3' primer has the sequence 5' GCAGCATCTAGATCAAAATGNTGGAAGCCGATTGTTTTCCGGTTTATCC 3' (SEQ ID NO: 36) containing the XbaI restriction site followed by a number of nucleotides complementary to the 3' noncoding sequence in Figures 4A-B (SEQ ID NO:10).

If a naturally occurring signal sequence is used to produce a secreted protein, the vector does not need a second signal peptide. Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence in an effort to secrete the protein from the cell. (See, e.g., WO 96/34891.)

The amplified fragment is then digested with the BglII and XbaI and purified on a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC4 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five µg of the expression plasmid pC4 is cotransfected with 0.5 ug of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 uM, 2 uM, 5 uM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 uM. Expression of full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

### **Example 7: Construction of N-Terminal and/or C-Terminal Deletion Mutants**

The following general approach may be used to clone a N-terminal or C-terminal deletion full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP deletion mutant.

- 5 Generally, two oligonucleotide primers of about 15-25 nucleotides are derived from the desired 5' and 3' positions of a polynucleotide of SEQ ID NO:1, 4, 7, or 10. The 5' and 3' positions of the primers are determined based on the desired full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide fragment. An initiation and stop codon are added to the 5' and 3' primers respectively, if necessary, to express the full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide fragment encoded by the polynucleotide fragment.
- 10 Preferred full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide fragments are those encoding the N-terminal and C-terminal deletion mutants disclosed above in the "Polynucleotide and Polypeptide Fragments" section of the Specification.

- 15 Additional nucleotides containing restriction sites to facilitate cloning of the full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide fragment in a desired vector may also be added to the 5' and 3' primer sequences. The full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide fragment is amplified from genomic DNA or from the deposited cDNA clone using the appropriate PCR oligonucleotide primers and conditions discussed herein or known in the art. The full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide fragments encoded by the full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide fragments of the present invention may be expressed and purified in the same general manner as the full length polypeptides, although routine modifications may be necessary due to the differences in chemical and physical properties between a particular fragment and full length polypeptide.
- 20

- 25 As a means of exemplifying but not limiting the present invention, the polynucleotide encoding the full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide fragment L-39 to N-889 is amplified and cloned as follows: A 5' primer is generated comprising a restriction enzyme site followed by an initiation codon in frame with the polynucleotide sequence encoding the N-terminal portion of the polypeptide fragment beginning with L-39. A complementary 3' primer is generated comprising a restriction enzyme site followed by a stop codon in frame with the polynucleotide sequence encoding C-terminal portion of the full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide fragment ending with N-889.
- 30

The amplified polynucleotide fragment and the expression vector are digested with restriction enzymes which recognize the sites in the primers. The digested polynucleotides are then ligated together. The full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide fragment is inserted into the restricted expression vector, preferably in a manner which places the full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide fragment coding region downstream from the promoter. The ligation mixture is transformed into competent *E. coli* cells using standard procedures and as described in the Examples herein. Plasmid DNA is isolated from resistant colonies and the identity of the cloned DNA confirmed by restriction analysis, PCR and DNA sequencing.

#### **Example 8: Protein Fusions of WF-HABP, OE-HABP, or BM-HABP**

Full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptides are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the half-life time in vivo. Nuclear localization signals fused to full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptides can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule..

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide, isolated by

the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

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GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCGTGCC
10 CAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCTCTTCCCCCAAAACCCAAG
GACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGTGGACGTAA
GCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGC
ATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGT
CAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC
15 AAGGTCTCCAACAAAGCCCTCCCAACCCCCATCGAGAAAACCATCTCAAAGCCAA
AGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTG
ACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACAT
CGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCC
TCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACA
20 AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCT
GCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGAGTGCGA
CGGCCGCGACTCTAGAGGAT (SEQ ID NO:37)

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#### **Example 9: Production of an Antibody**

25 The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) For example, cells expressing full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP is administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP protein is prepared and purified to render it

30 substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared



using hybridoma technology. (Köhler et al., *Nature* 256:495 (1975); Köhler et al., *Eur. J. Immunol.* 6:511 (1976); Köhler et al., *Eur. J. Immunol.* 6:292 (1976); Hammerling et al., in: *Monoclonal Antibodies and T-Cell Hybridomas*, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide or, more preferably, with a secreted full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56 degree C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 ug/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (*Gastroenterology* 80:225-232 (1981).) The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide.

Alternatively, additional antibodies capable of binding to full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP specific antibody can be blocked by full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP. Such antibodies comprise anti-idiotypic antibodies to the full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP specific antibody and can be used to immunize an animal to induce formation of further full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP specific antibodies.

It will be appreciated that Fab and F(ab')<sub>2</sub> and other fragments of the antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). Alternatively, secreted full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

**Example 10: Method of Detecting Abnormal Levels of full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP in a Biological Sample**

Full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptides can be detected in a biological sample, and if an increased or decreased level of full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies to full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 11. The wells are blocked so that non-specific binding of full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with

deionized or distilled water to remove unbounded full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP .

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP in the sample using the standard curve.

#### **Example 11: Formulating a Polypeptide**

The full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP administered parenterally per dose will be in the range of about 1ug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier"

5 refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP is also suitably

10 administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22:547-556 (1983)), poly (2-hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and R. Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D-(-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptides. Liposomes containing the full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP are prepared by methods known

15 per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. USA 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent

20 cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations

30 employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

Generally, the formulations are prepared by contacting full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

Full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the

lyophilized full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP may be employed in conjunction with other therapeutic compounds.

#### **Example 12: Method of Treatment Using Gene Therapy - In Vivo**

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP sequences into an animal to increase or decrease the expression of the full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide. The full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide may be operatively linked to a promoter or any other genetic elements necessary for the expression of the full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata H. et al. (1997) Cardiovasc. Res. 35(3):470-479, Chao J et al. (1997) Pharmacol. Res. 35(6):517-522, Wolff J.A. (1997) Neuromuscul. Disord. 7(5):314-318, Schwartz B. et al. (1996) Gene Ther. 3(5):405-411, Tsurumi Y. et al. (1996) Circulation 94(12):3281-3290 (incorporated herein by reference).

The full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral

sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotides may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to

about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polynucleotide in muscle *in vivo* is determined as follows. Suitable full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP template DNA for production of mRNA coding for full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP polypeptide is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15  $\mu$ m cross-section of the individual quadriceps muscles is histochemically stained for full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP protein expression. A time course for full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be used to extrapolate



proper dosages and other treatment parameters in humans and other animals using full-length WF-HABP, WF-HABP, OE-HABP, or BM-HABP naked DNA.

### **Example 13: WF-HABP , OE-HABP, and BM-HABP Expression in Human Tissues and Cells**

As a first step toward characterizing the expression pattern of the gene encoding the novel WF-HABP protein, the WF-HABP mRNA expression levels in various human tissues and cells was examined by Northern blotting analysis. WF-HABP mRNA was detectable in all the human tissues examined with very low levels detected in the brain and kidney. The highest level of expression was observed in the heart, placenta and lung, with lower levels found in the liver, pancreas, and skeletal muscle. Four major transcripts of 9.5, 4.5, 3.0 and 2.4 Kb were detected. The 9.5 Kb band appeared to be the predominant mRNA and was especially prominent in the placenta and the heart. OE-HABP mRNA was detected in lung, placenta, and heart, with highest expression observed in the lung as a 2.2 Kb transcript. BM-HABP mRNA was apparent only in the liver and appeared as a smear between 5 and 2 Kb. The expression of BM-HABP was also analyzed in human fetal brain, lung, liver and kidney and found that a distinct 9.5 Kb mRNA was expressed at an elevated level in fetal liver with a low level of signal also observed the lung.

The expression pattern of WF-HABP, OE-HABP, and BM-HABP was also examined in human smooth muscle cells (SMCs), human fetal lung fibroblasts (ETL), human umbilical vein endothelial cells (HUVECs), as well as in HL-60 and U937 cells. WF-HABP mRNA expression was not detected in either uninduced or TPA-stimulated HL-60 cells. A minor 2.4 Kb band was detected in all of the other cell types examined. Induction of U937 cells with TPA resulted in a slight decrease of the signal. However, it is noteworthy that WF-HABP mRNAs of 9.5, 4.5 and 3.0 Kb were expressed exclusively by HUVECs.

The 2.2 Kb OE-HABP transcript identified supra was expressed by both HUVECs and SMCs, but not by ETLs, HL60 or U937 cells. Interestingly, U937 cells responded to stimulation with TPA by expressing a major new 4.3 Kb transcript and minor bands of 3.8, and 3 Kb. There was no detectable mRNA expression of BM-HABP in any of the above cell lines.

Given that endothelial cells express a unique set of WF-HABP mRNA transcripts the expression of this gene was analyzed in HUVECs in greater detail. We first examined whether short-term stimulation of endothelial cells with FGF-1, EL-1 and PNIA could alter mRNA

expression of WF-HABP and found that HUVECs treated with these factors for up to four hours did not substantially alter the expression of this gene. However, growth-arrested HUVECs were consistently observed to express a high level of WF-HABP mRNA that decreased dramatically when the cells were induced to proliferate with FGF-1.

5        Conditions for culturing and preparing cells for the above Northern blotting experiments are described *infra*. BL-60 (human peripheral blood promyelocytic leukemia, ATCC CCL 240) and U937 (human histocytic lymphoma, ATCC CRL 1593) were obtained from the American Type Culture Collection (Rockville, MD). Cells were grown in RPMI 1640, supplemented with 10% Fetal Bovine Serum (FBS). HFLI (human diploid fetal lung  
10    fibroblasts, ATCC CCL 153) were obtained from American Type Culture Collection (Rockville, MD), and SMC (human saphenous vein smooth muscle Cells)<sup>7</sup> were kindly provided by Dr. Peter Libby (Tufts University School of Medicine, Boston, MA). Cells were grown in DMEM and M-199 respectively, complemented with 10% FBS. HUVECs (human umbilical vein endothelial cells), strain H101, were a generous gift from Dr. Susan Garfinkel  
15    (Dept. of Molecular Biology, ARC, Rockville, NED). Cells were grown in M-199 containing 10% FBS, supplemented with FGF1/Heparin. BL-60 and U937 cells were grown under conditions as known by the skilled artisan for 2 days and then induced with 0.15 ug/ml of 12-0-tetradecanoylphorbol-13-acetate (TPA) for 72 hr to elicit a differentiation response. HUVECs were growth arrested for 48hr in complete media with 10% serum without FGF-1/Heparin.

20        Conditions for Northern Blot hybridization are described *infra*. Total RNA were isolated from cultured cells by selective retention on a silica gel-based membrane with RNeasy Mini Kit (Qiagen Inc, Valencia, CA). Briefly, cells were lysed and homogenized under highly denaturing conditions in the presence of guanidinium isothiocyanate. Total RNA was separated from contaminating proteins and DNA by centrifugation and subsequently eluted from the  
25    column with water. Five micrograms of purified total RNA per lane were size-fractionated on a 1% agarose gel containing, 0.5M formaldehyde, transferred to Zetabind nylon membrane (AMF/Cuno, Inc., Meriden, CN) by electroblotting, and UV crosslinking. Immobilized RNA was hybridized at 55°C overnight with 1 to 5x10<sup>6</sup> cpm/ml of  $\alpha$ -<sup>32</sup>P dCTP-labeled cDNA probes prepared by random primed DNA labeling (Boehringer Mannheim GmbH, Germany).  
30    Following hybridization, membranes were washed with increasing stringency at 55°C, 2x15 min in each of the following buffers. Wash Buffer A: 0.5% BSA, 5% SDS, 40mM NaH<sub>2</sub>PO<sub>4</sub>, 1mM EDTA; Wash Buffer B: 1% SDS, 40mM NaH<sub>2</sub>PO<sub>4</sub>, 1mM EDTA; 0.2xSSPE. Blots were air dried and exposed to Kodak X-Omat AR film (Eastman Kodak Company, Rochester, NY)

at -80°C. 800bp human glyceraldehyde-3-phosphate dehydrogenase (GAPDH) cDNA was used as a control probe.

Blots, containing mRNA obtained from human heart, brain, placenta, lung, liver, skeletal muscle, kidney and pancreas, were acquired from Clontech (Palo Alto, CA). These blots were probed for the WF-HABP, OE-HABP, and BM-HABP message and also hybridized with GAPDH cDNA control probe.

#### **Example 14: WF-HABP Expression In vivo**

Northern analysis revealed a high level of WF-HABP mRNA expression in vessel-rich human tissues including the heart and the placenta. Furthermore, *in vitro* analysis (Example 13, supra) revealed predominant expression of this message in cultured endothelial cells. Therefore, *in situ* hybridization was performed in the placenta to identify the cells that expressed WF-HABP mRNA. Hybridization signal was detected in cells lining fetal blood vessels and capillaries found inside terminal villi. Syncytial trophoblasts, composing the external layer of the terminal villi, were always negative. Using immunohistochemistry, this pattern was identical in sections stained for the endothelial specific antigen (CD31), suggesting that the major cell type in the placenta expressing WF-HABP are endothelial cells. We also examined the brain and found it expressed a very low level of WF-HABP mRNA when probed by Northern blotting. *In situ* hybridization generally confirmed a lack of WF-HABP positive cells in the brain with the exception of weak signals around small blood vessels and capillaries. CD31 staining revealed a similar, although more prominent, expression pattern.

The expression pattern of WF-HABP was examined in other vascular tissues including human aorta and atherectomy specimens. Positive RNA signal was apparently observed only in endothelial cells lining microvessels in the adventitia and in the medial layer of the aorta. No signal was detected in smooth muscle cells of the medial layer. Specificity was confirmed by the absence of the signal when hybridization was performed without probe or with a corresponding sense probe. We did observe non-specific staining of collagen fibers in the adventitia with both the sense and antisense probes, likely due to the binding of anti-digoxigenin antibody to collagen. To confirm that cells expressing WF-HABP mRNA were indeed endothelial cells, immunohistochemical analysis on adjacent sections of the same specimen was performed using an antibody that specifically recognizes CD31. The signal for CD31 antigen was found to be distributed in an analogous manner to that for WF-HABP.

The expression of WF-HABP mRNA in human atherosclerotic lesions was examined. A strong WF-HABP-specific signal was found in vessel-abundant regions of the specimens. Again, this signal co-localized with the distribution of EC-specific CD31 antigen. No signal was detected in SMC or in macrophage rich regions. However, sporadic appearance of positive stellate cells was observed in otherwise negative myxomatous tissue. In can be concluded from these studies that WF-HABP mRNA is expressed predominantly by endothelial cells in various tissues and its expression is especially prominent in diseased blood vessels.

The conditions for In situ hybridization are described infra. Non-radioactive In Situ hybridization was performed on paraffin-embedded human tissues and atherectomy specimens. WF-HABP m.RNA probes (sense and antisense) were labeled with digoxigenin-11-uridine-5'-triphosphate (Boehringer Mannheim GrnbH, Germany) via in vitro transcription (Dig RNA labeling kit, Boehringer Mannheim GmbH, Germany).

The tissues were cut into serial 5-um thick sections onto silanized double-positive glass slides (Fisher Scientific, Pittsburgh, PA). Tissue sections were deparaffinized for 60 min at 60°C, washed extensively in xylene and rehydrated in decreasing ethanol series. Endogenous peroxidase was quenched in PBS containing 3% H<sub>2</sub>O<sub>2</sub> for 20 min. To facilitate probe penetration, tissue sections were deproteinized in 2mg/ml pepsin solution in 0.2N HCl (Nuovo). Sections were equilibrated, prehybridized and hybridized according to the SureSite II System Manual (Novagen, Inc., Madison, WI). Hybridization was carried out for 18 hrs in a humid chamber at 50°C; probe concentration was 1ng/ul.

After hybridization, sections were subjected to successively stringent washes as follows: 2xSSC 30 min at 50°C; 2xSSC containing 0.02ug/ml RNase A, 30 min at 37°C; 2xSSC containing 50% formamide, 30 min at 50°C; 2 washes with 1xSSC containing 0.067% sodium paraphosphate, 30 min each at 50°C.

Signal amplification was carried out according to Tyramide Signal Amplification for chromogenic Situ hybridization (TSA-Indirect) protocol (NEN Life Science Products, Boston, MA). TNT wash buffer contained 0.05% TWEEN-20 in PBS, and TNB blocking buffer was comprised of 0.5% blocking reagent in PBS. Anti-digoxigenin antibody (sheep Fab fragments conjugated with horseradish peroxidase (POD), Boehringer Mannheim GmbH, Germany) was diluted 1-50 in TNB. Signal was visualized with DAB (diaminobenzidine) substrate kit (Vector Laboratories, Inc., Burlingame, CA). Myer's Hematoxylin was used to counterstain the sections.

To confirm reliability of the method, protamine antisense probe was hybridized to sections of mouse testes as a positive control in each experiment. Also, sense WF-HABP probe, as well as hybridization without any probe, were used as negative controls in each experiment.

5           Conditions for immunohistochemistry are described infra. Paraffin-embedded serial 5um-thin sections of the human tissues analyzed by Northern blotting and several atherectomy specimens (described in Example 13) were used. Endogenous peroxidase activity was quenched in methanol with 0.3%  $H_2O_2$ . The sections were reacted for 1hr at room temperature with a monoclonal mouse anti-human CD31 antibody specific for endothelial cells (DAKO, 10   Denmark). Antibodies were diluted 1-50 in PBS containing 10% normal horse serum and 1% bovine serum albumin. Primary antibody was detected by the indirect avidin-biotin-horseradish peroxidase method (ABC elite kit, Vector Laboratories, Inc., Burlingame, CA). Normal mouse IgG (1: 1000) were used as negative controls. Myer's Hematoxylin was used to counterstain the sections.

15           **Example 15: Identification and Characterization of Three Novel Hyaluronan-Binding Protein Encoding Genes: Endothelial Cell-Specific Expression of One Gene**

20           It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

25           The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference.

          Moreover, the sequence submitted herewith in paper and computer readable form are herein incorporated by reference in their entireties.